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STUDIES ON STREPTOMYCIN IN MAN. I. ABSORPTION, DISTRIBUTION, EXCRETION AND TOXICITY. By HAROLD A. ZINTEL, M.D., HARRISON F. FLIPPIN, M.D., ANNA C. NICHOLS, MARJORIE M. WILEY, and J. E. RHOADS, M.D. 421

CASE OF STREPTOCOCCUS VIRIDANS PNEUMONIA SUCCESSFULLY TREATED WITH PENICILLIN. By MAJOR SAUL SOLOMON, M.C., A.U.S. 431

OBSERVATIONS ON THE CONTINUOUS INTRAMUSCULAR METHOD OF ADMINISTERING PENICILLIN. By HAROLD L. HIRSH, M.D., and HARRY F. DOWLING, M.D. . . . 435

ELECTROCARDIOGRAPHIC OBSERVATIONS IN NORMAL THYROIDECTOMIZED AND THIOUREA TREATED RATS. By ROBERT K. WALLER, and HARRY A. CHARIPPER. With the technical assistance of ALBERT H. STENGER. 443

A STUDY OF THE RELATIONSHIP OF THE BASAL BODY TEMPERATURE TO THE BASAL METABOLIC RATE IN HOSPITALIZED PATIENTS. By CAMPBELL MOSES, M.D. . 453

THE DANGER OF CONTINUED ARSENOTHERAPY IN CASES OF ERYTHEMA OF THE NINTH DAY. By MAJOR WILLIAM LEIFER, M.C., A.U.S. 458

POSSIBLE EFFECTIVENESS OF THE L. CASEI FACTOR ("FOLIC ACID") CONCENTRATES ON REFRACTORY ANEMIA AND LEUKOPENIA, WITH PARTICULAR REFERENCE TO LEUKOPENIA FOLLOWING RADIATION THERAPY. By C. J. WATSON, W. H. SEBRELL, J. L. McKELVEY, and F. S. DAFT. With the technical assistance of VIOLET HAWKINSON. 463

SYNCHRONIZATION OF NEUROTIC BEHAVIOR PATTERNS. By EDMUND BERGLER, M.D. 470

ATRIAL SEPTAL DEFECT. STUDY OF HEMODYNAMICS BY THE TECHNIQUE OF RIGHT HEART CATHETERIZATION. By EMMETT S. BRANNON, M.D., H. STEPHEN WEENS, M.D., and JAMES V. WARREN, M.D. 480

IDIOPATHIC (?) HYPOPROTHROMBINEMIA. REPORT OF A CASE. By V. THOMAS AUSTIN, M.D., and HENRY QUASTLER, M.D. 491

APLASTIC ANEMIA TERMINATED BY REMOVAL OF A MEDIASTINAL TUMOR. By GEORGE H. HUMPHREYS, II, M.D., and HAMILTON SOUTHWORTH, M.D. 501

SALMONELLA APPENDICITIS. By A. DANIEL RUBENSTEIN, M.D., and BEN B. JOHNSON, M.D. 517

PROGRESS OF MEDICAL SCIENCE:

DERMATOLOGY AND SYPHILOLOGY: BIOLOGIC FALSE POSITIVE REACTIONS TO THE TESTS FOR SYPHILIS. By HERMAN BEERMAN, M.D. 524

OTO-RHINO-LARYNGOLOGY: CANCER OF THE MOUTH: ITS PRESENT DAY TREATMENT. By WALTER MAYNE, M.D. 548

Contents continued on adv. page 10

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THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

OCTOBER, 1945

ORIGINAL ARTICLES

STUDIES ON STREPTOMYCIN IN MAN

I. ABSORPTION, DISTRIBUTION, EXCRETION AND TOXICITY*†

BY HAROLD A. ZINTEL, M.D.
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NUMEROUS clinical studies have shown that penicillin possesses remarkable activity against gram-positive bacteria but has no effect on the gram-negative bacilli as a group. Because penicillin is definitely restricted in the range of its antibacterial activities, considerable interest is being focused on other chemotherapeutic agents. Among those of particular interest is the substance obtained from a certain strain of *Actinomyces griseus* called streptomycin. This substance, first described by Waksman,[1,2] is characterized by limited toxicity to animals[3] and by high activity *in vivo*[4,5,6,7] against various gram-positive and gram-negative bacteria.

As a necessary preliminary to the extensive use of this substance, certain studies were undertaken to determine the behavior of streptomycin in patients and to determine the possibility of toxic or side reactions. Two series of experiments, one dealing with the fate of a single dose and the other with the response to multiple doses, are reported in this paper.

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

† The Streptomycin was kindly supplied to us by Merck & Co., Rahway, N. J.

Methods and Materials. Streptomycin concentration was determined by the plate cup method described by Stebbins and Robinson.[8] The fate of a single dose of streptomycin, administered by various routes was studied in 20 patients who for the most part fell into no specific disease category and varied from healthy to seriously ill individuals. Continuous administration of streptomycin was studied in 18 patients suffering from a variety of diseases, including typhoid fever, Rocky Mountain spotted fever, brucellosis, ulcerative colitis, urinary tract infection and *Salmonella oranienburg* infection. When administered orally, the drug was dissolved in sterile water and mixed with milk. For continuous intravenous administration, streptomycin was given in in a continuous drip of 5% glucose solution. When a large amount of streptomycin, such as 600,000 units, was given intravenously in a single dose, it was dissolved in 200 cc. of physiologic saline solution and administered over a period of 15 to 20 minutes. For intramuscular injection the streptomycin was dissolved in 1% procain solution to a concentration of 40,000 or 100,000 units of streptomycin per cc. of solution.

All of the patients receiving streptomycin were followed closely for possible toxic reactions. In a subgroup of 10 patients, more extensive studies were undertaken to determine any possible detrimental effects upon the liver, kidney and the blood.

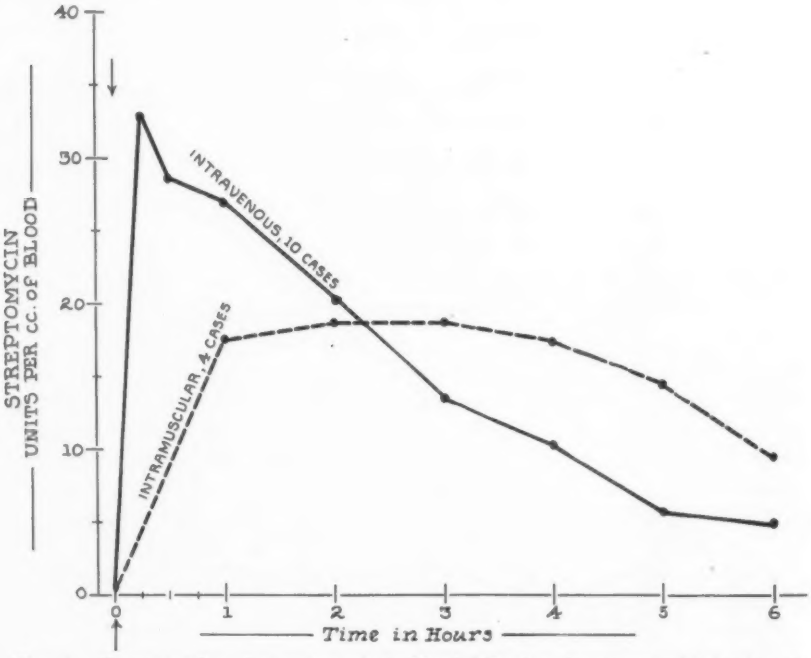

FIG. 1.—Concentration of streptomycin in blood following the parenteral injection of 600,000 units.

INTERMITTENT PARENTERAL ADMINISTRATION. Following the intravenous injection of a single dose of 600,000 units of streptomycin, the drug concentration in the blood decreases at a more or less uniform rate for 6 hours (Fig. 1). Fifteen minutes after administration of the streptomycin, the average blood streptomycin level was 32.8 units.

At the end of 6 hours, a small amount of streptomycin, 4.9 units per cc., is still detectable in the blood in the majority of instances.

When the same amount of streptomycin is administered as a single dose subcutaneously in 1% procain solution, the maximum blood level is not attained until between 2 and 3 hours. The maximum streptomycin blood level attained following intramuscular injection was not so high as was obtained following the intravenous injection of 600,000 units. If streptomycin is administered every 3 hours, an additive effect is obtained. In 1 patient who received 375,000 units every 3 hours by intramuscular injection, or a total of 3,000,000 units every 24 hours, the blood streptomycin levels after the 3rd day of administration usually varied between 20 and 60 units per cc. of blood.

Continuous Intravenous Infusion. When 3,000,000 units of streptomycin in 3000 cc. of a 5% glucose solution were administered daily by the continuous intravenous infusion method, the blood streptomycin levels usually varied between 20 and 60 units of streptomycin per cc. of blood. The blood streptomycin level during the administration of 1,000,000 units of streptomycin by the continuous intravenous or intramuscular methods varied between 10 and 20 units per cc. of blood. The rate of excretion of streptomycin in the urine was fairly uniform. In the average case two-thirds of the amount administered by continuous intravenous infusion was recovered in the urine. Approximately 2% was recovered in the feces.

Oral Administration. Streptomycin was administered orally at the rate of 1,000,000 units per day to 6 patients. Most of the drug was recovered in the feces. The concentration of streptomycin in the feces increases rapidly during the first few days of treatment. After 4 days of treatment, the stool concentration of streptomycin was usually between 1000 and 5000 units per gram of feces. One specimen from a patient who had received 1,000,000 units daily by mouth for 6 days had a fecal concentration of 9000 units of streptomycin per gram of feces. Only occasionally was any streptomycin found in the blood, and then it was found in minimal amounts, namely 1 to 6 units per cc. of blood. Occasionally measurable levels of streptomycin were found in the urine following the oral administration of 1,000,000 units in 4 cases.

It is obvious that streptomycin passes through the gastro-intestinal wall with difficulty, since when given orally very little appears in the blood, and when administered intravenously only very small amounts of streptomycin are found in the gastro-intestinal tract. It would then seem appropriate to treat those infections in which the pathogenic organisms are found both in the gastro-intestinal tract and in the blood stream by the oral and parenteral routes.

Excretion. Streptomycin when administered intravenously, subcutaneously or intramuscularly is excreted largely in the urine. Only about 2% of the drug was found in the feces. In 10 cases the urinary excretion of streptomycin was followed for a period of 24 hours after the administration of a single intravenous dose of 600,000 units. From 29 to 89% of streptomycin was excreted in the urine in 24 hours

(Fig. 2). The average 24 hour urine excretion was 66%. Except in those patients who had reduced renal function, the amount of streptomycin excreted varied proportionally to the urine volume.

The highest urine concentration of the samples taken 3 hours after the injection of 600,000 units of streptomycin was 520 units per cc. with an average level for all 10 cases of 353 units per cc. of urine. At the end of 24 hours, the average concentration was 16 units of streptomycin per cc. of urine. It would appear from the curves of the urine concentration and the urinary excretion of streptomycin (Fig. 2) that

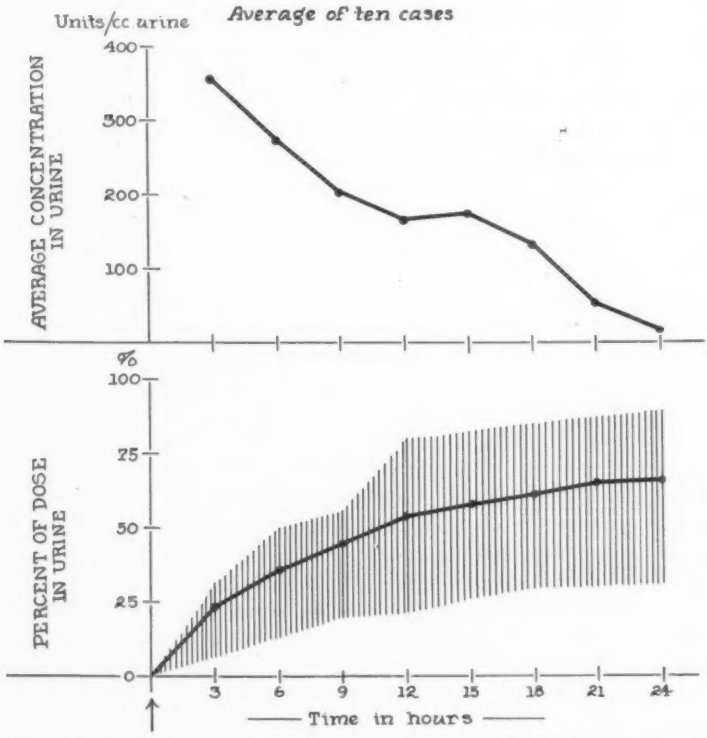

FIG. 2.—Urinary excretion of streptomycin following a single intravenous dose of 600,000 units.

very little more streptomycin would have been recovered if the studies had been carried on more than 24 hours. Therefore, since only 2% of parenterally administered streptomycin is excreted in the feces, and only approximately 66% of the injected amount appears in the urine, it seems logical to presume that some of the streptomycin is retained or destroyed in the body. As stated before, when the drug is administered orally, the chief route of excretion is in the feces.

DISTRIBUTION OF STREPTOMYCIN IN VARIOUS BODY FLUIDS. *Peritoneal Fluid.* Streptomycin appears in peritoneal fluid following both intravenous and intramuscular administration. Figure 3 shows the

rate of appearance of streptomycin in peritoneal fluid following the administration of a single intravenous dose of 600,000 units. Streptomycin first appeared in the peritoneal fluid ½ hour after the drug was administered, and thereafter the concentration of streptomycin increased while the blood streptomycin level was decreasing. This first patient had ascites secondary to cirrhosis of the liver.

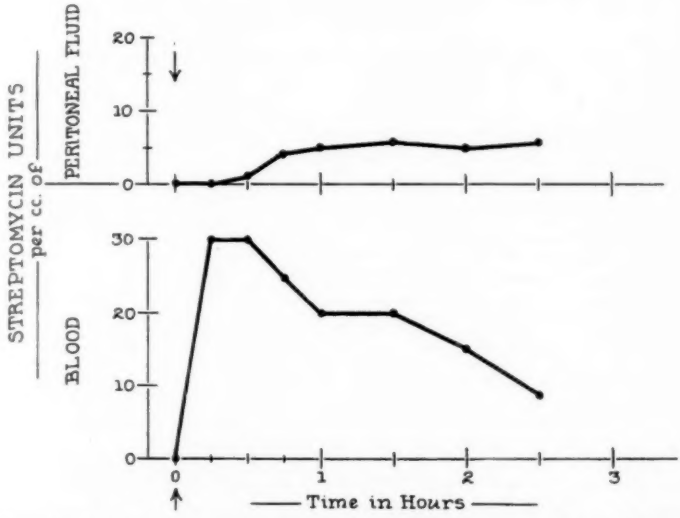

FIG. 3.—Diffusion of streptomycin into peritoneal fluid following a single intravenous injection of 600,000 units.

Streptomycin, 125,000 units intramuscularly every 3rd hour, was administered to a second patient with ascites secondary to carcinomatosis. At the end of 24 hours, the peritoneal fluid level was 23 units per cc., and at the same time the blood level was 15 units per cc. When streptomycin is administered parenterally for longer than a few hours, the blood and peritoneal streptomycin levels are approximately equal. Murphy and Ravdin[9] have shown that streptomycin enters the peritoneal cavity both in the normal animal and in animals with peritonitis. Often the peritoneal fluid streptomycin levels were as high or higher than the blood levels at the corresponding time. The results which they have obtained following the treatment of experimental peritonitis in animals with streptomycin have been good.

Pleural Fluid. Three patients with pleural effusions were given streptomycin either by the intramuscular or intravenous routes, and then samples of blood and pleural fluid were obtained simultaneously for determination of their streptomycin content (see Table 1). Streptomycin was found in the pleural fluid of all patients tested. Fifteen minutes following a single intravenous injection of 600,000 units when the blood streptomycin content was 30 units per cc., no streptomycin was found in the pleural fluid. Two hours after the administration of the drug there were 6 units of streptomycin per cc. of pleural fluid. At

the same time a level of 15 units per cc. was found in the blood. When streptomycin was administered over 24 hours, higher pleural fluid concentrations were found. Two patients were given 125,000 units of streptomycin intramuscularly every 3 hours for 24 hours. At the end of the 24 hours, the concentrations found were 18 and 7 units per cc. of pleural fluid. The blood levels in these 2 patients at the time the pleural fluid samples were obtained were 15 and 20 units per cc. respectively.

TABLE 1.—COMPARISON OF BLOOD AND PLEURAL FLUID STREPTOMYCIN LEVELS

Patient	Dose, units	Route	Time interval in minutes from last dose	Blood level, units per cc.	Pleural fluid level, units per cc.
1 . . .	125,000 every 3 hrs. for 8 doses	I.M.	120	15	18
2 . . .	125,000 every 3 hrs. for 8 doses	I.M.	90	20	7
3 . . .	600,000 single injection	I.V.	15	30	0
3 . . .	600,000 single injection	I.V.	120	15	6

Bile. Following a single intravenous dose of 600,000 units of streptomycin, maximum bile levels varying between 3 and 7.5 units per cc. have been found, as is shown in Figure 4. At the time these bile specimens were obtained, the streptomycin blood levels were 18 units per cc. in each patient. In 1 patient who received 125,000 units every 3 hours by intramuscular injection for 24 hours, the bile contained 10 units of streptomycin per cc. at the end of the 24 hour period. During the 24 hours, the bile was collected by means of a choledochostomy tube and constant suction. This method has been used in the past for total bile excretion studies. The 24 hour output of streptomycin in the bile in this patient was 3500 units.

TABLE 2.—COMPARISON OF BLOOD AND CEREBROSPINAL FLUID STREPTOMYCIN LEVELS

Patient	Total daily dose in units	Duration of treatment	Route	Blood units, per cc.	Cerebrospinal fluid units, per cc.
1 . .	600,000 single injection	2 hrs.	I.V.	6.0	0.0
2 . .	2,000,000	5 days	I.M.	17.0	1.0
3 . .	3,000,000	6 days	I.M.	27.0	1.0
4 . .	1,000,000	24 hrs.	I.M.	13.0	5.0
5 . .	1,000,000	24 hrs.	I.V.	..	25.0

Cerebrospinal Fluid. Streptomycin spinal fluid levels were determined in 5 patients (Table 2). Four of these patients had no evidence of cerebrospinal disease. One of these normal patients (No. 1) was given a single intravenous injection of 600,000 units of streptomycin. Two hours later there was no streptomycin in the cerebrospinal fluid. The 3 remaining patients (Nos. 2, 3 and 4) with apparently normal cerebrospinal systems received from 1,000,000 to 3,000,000 units daily

by intermittent intramuscular injections. The levels obtained in these patients varied between 1 and 5 units per cc. of spinal fluid. One infant (No. 5) with *Hemophilus influenzæ* meningitis had a spinal fluid level of 25 units per cc. after having received 1,000,000 units over 24 hours. The blood levels of the patients at the time the spinal fluid specimens were obtained are shown in Table 2.

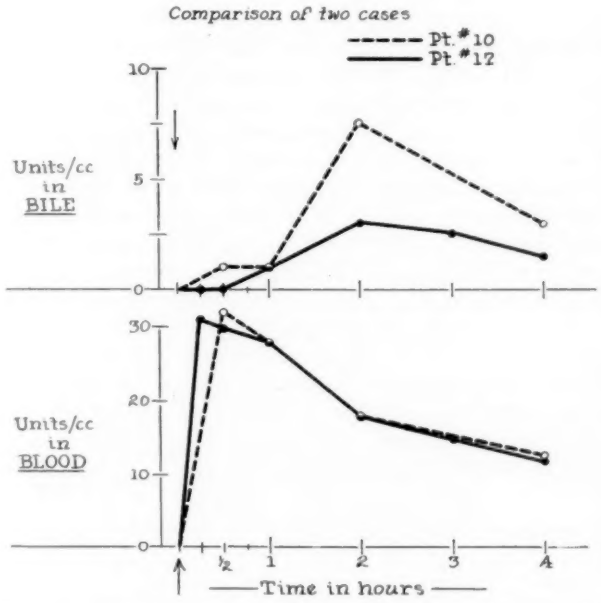

FIG. 4.—Excretion of streptomycin in the bile following a single intravenous injection of 600,000 units.

Ocular Fluids. Leopold[10] has demonstrated streptomycin in both the aqueous and vitreous humors of the eye following intravenous, intramuscular and local administration of streptomycin in animals. In 1 patient with glaucoma, 3 units of streptomycin were found per cc. of aqueous humor 30 minutes following the intravenous administration of 600,000 units of streptomycin. A blood specimen taken at the same time contained 40 units of streptomycin per cc. of blood. The secondary aqueous humor removed 3 hours later from the same eye contained 18 units of streptomycin per cc. of aqueous humor.

Fetal Blood and Amniotic Fluid. Streptomycin does enter the fetal cord blood and the amniotic fluid. Several patients in labor at term were given 250,000 units of streptomycin either by the intramuscular or intravenous routes. Specimens of fetal cord blood, maternal blood and amniotic fluid were obtained at the time of delivery. In 1 patient the streptomycin concentration was 8 units per cc. of maternal blood, 9 units per cc. of cord blood and 7 units per cc. of amniotic fluid 2 hours after the intravenous injection of 250,000 units. This work will be reported by Woltz and his associates.[11]

Toxic Effects. *Immediate Effects.* The immediate toxic effects have been headache, flushes, transient urticaria and fever. They have been of mild to moderate severity and can be avoided to a large extent by slowing the rate of administration. Local thrombophlebitis may occur after continuous intravenous administration. A single case evidenced flushing of the skin, palpitation and severe throbbing headache when a second course of the drug was started 10 days after the first course was stopped. This same patient had no reactions whatsoever when a more purified form of the drug was used.

Effect of a Single Massive Dose of Streptomycin on Liver Function. In 6 patients an attempt was made to determine whether or not there was any evidence of hepatic damage following the intravenous injection of 600,000 units of streptomycin in a single dose. Estimation of possible liver damage was made by determinations of the prothrombin time; quantitative van den Bergh; total serum cholesterol; serum cholesterol—cholesterol ester ratio; hippuric acid conjugation, bromsulphthalein excretion, cephalin flocculation, thymol turbidity and colloidal gold tests. In all 6 patients these determinations were made 24 hours before a single test dose of 600,000 units of intravenous streptomycin, and the tests were repeated 24 hours after the administration of the streptomycin. Exceptions were in the case of the cephalin flocculation, thymol turbidity and colloidal gold tests which were not repeated until 48 hours after the streptomycin was given. The values obtained are shown in Table 3.

Table 3.—Effect of the Intravenous Injection of 600,000 Units of Streptomycin on Liver Function

Patient:	1	2	3	4	5	6	Average
Bromsulphthalein retention, %:							
Before	0	0	0	10	0	10	
After	0	0	0	5	0	5	
Hippuric acid conjugation,gm. excr.:							
Before	1.6	1.7	2.0	2.1	1.5	..	1.77
After	1.4	1.2	1.6	1.4	1.6	..	1.29
Van den Bergh, mg. of bilirubin:							
Before	0.6	0.3	0.7	0.4	0.5	0.5	0.33
After	0.5	0.4	0.4	0.2	0.4	0.2	0.35
Cholesterol, mg. %:							
Before	167	171	86	138	123	156	142
After	157	155	105	182	147	161	151
Cholesterol in esterified form, %:							
Before	58	65	57	59	66	56	60
After	58	61	64	73	67	57	63
Cephalin flocculation:							
Before	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
After	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
Colloidal gold:							
Before	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
After	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
Thymol turbidity:							
Before	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
After	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
Prothrombin, % of normal:							
Before	80	90	95	70	75	55	77.5
After	80	100	75	70	95	70	81.7

Two of the patients studied had liver damage prior to the administration of the test dose of streptomycin as judged by the bromsulphthalein retention test. Neither of these 2 patients showed evidence of further liver damage after the administration of the streptomycin.

In fact both of the patients showed a slight decrease (which was probably insignificant) in the amount of bromsulphthalein which was retained after the test dose of streptomycin. The other liver tests performed were all within normal limits.

Effect of a Massive Dose of Streptomycin on Renal Function. Tests of renal function were made on 6 patients before and after the administration of 600,000 units of streptomycin in a single dose intravenously. Blood urea nitrogen, blood non-protein nitrogen and urea clearance tests were performed 24 hours before and were repeated 24 hours after the administration of the streptomycin. The results are shown in Table 4. Changes in the various values obtained were irregularly distributed between increases and decreases so that the averages of the figures obtained in the 6 patients were about the same before and after the administration of streptomycin. In addition, in 12 patients urinalyses were made at 3 hour intervals for a period of 24 hours following the intravenous administration of 600,000 units of streptomycin. There was no evidence of renal damage as judged by the number of red blood cells, white blood cells, epithelial cells or casts in these examinations.

TABLE 4.—EFFECT OF THE INTRAVENOUS INJECTION OF 600,000 UNITS OF STREPTOMYCIN ON RENAL FUNCTION

Patient:	1	2	3	4	5	6	Average
Urea clearance % of average normal:							
Before	..	44	..	107	66	90	76.7
After	..	42.5	..	63	78	93	69.1
Blood urea nitrogen:							
Before	13.3	15	16	7	7	7	10.7
After	10.8	9.5	9.8	9	8	8	9.2
Non-protein nitrogen:							
Before	28	26	23	27	22	20	24.3
After	26	23	25	25	23	25	24.5

Effect of Streptomycin on Blood. Platelet, white blood cell and differential white blood cell counts, as well as hemoglobin determinations, were made 24 hours before and 24 hours after the intravenous administration of a single dose of 600,000 units of streptomycin (see

TABLE 5.—EFFECT OF THE INTRAVENOUS ADMINISTRATION OF 600,000 UNITS OF STREPTOMYCIN ON THE BLOOD

Patient:	1	2	3	4	5	6	7	8	9	10	Average
Hemoglobin:											
Before	77	97	89	82	78	80	74	97	89	93	85.6
After	85	96	84	74	75	69	70	95	86	88	82.2
White blood cell count:											
Before	8000	9500	9,300	5000	5500	7000	5400	8700	4000	6000	6840
After	7700	5600	14,200	7400	6600	6000	5800	6400	4000	6200	6990
Neutrophils:											
Before	75	81	68	56	66	68	79	72	78	74	71.7
After	60	70	79	78	66	66	69	81	66	75	71.0
Lymphocytes:											
Before	23	16	19	64	34	32	21	26	18	26	27.9
After	36	28	13	28	28	24	30	19	34	24	26.4
Eosinophils:											
Before	0	1	1	0	2	0	0	0	0	0	0.4
After	0	0	2	0	6	3	0	0	0	1	1.2
Basophils:											
Before	0	0	0	0	0	0	0	0	0	0	0
After	0	0	0	0	0	0	0	0	0	0	0
Monocytes:											
Before	2	2	12	0	0	0	0	0	0	0	1.6
After	4	2	6	4	0	7	1	0	0	0	2.4

Table 5). The changes in the values obtained were variable, however, the average of the values obtained before and after the administration of streptomycin was not significantly different. There was no evidence of toxicity as judged by these examinations of the blood picture.

Summary. 1. The blood level of streptomycin following single intravenous injections is better maintained than in the case of penicillin.[12] Detectable amounts were usually present for 6 hours as compared with $2\frac{1}{2}$ to 3 hours in the case of penicillin even when the intramuscular route was used for the latter drug.

2. The principal route of excretion for streptomycin after parenteral injection appears to be the urinary tract.

3. Following parenteral injection, the drug is distributed throughout most body fluids: blood, urine, ascitic fluid, pleural fluid, aqueous humor, vitreous humor, amniotic fluid and bile. Small amounts of the drug appeared in the spinal fluid in healthy individuals, but in a single case of *Hemophilus influenzæ* meningitis the spinal fluid contained 25 units per cc.

4. Relatively little transfer of streptomycin occurs between the blood and the lumen of the gastro-intestinal tract in either direction.

5. Following oral administration, levels as high as 9000 units per gm. were found in the feces.

6. Owing to the poor transfer of the drug across the walls of the alimentary tract, it would seem appropriate to use the drug both orally and parenterally in the treatment of infections such as those in which the pathogenic organisms are found both in the gastro-intestinal tract and in the blood stream.

7. Early side reactions have not been alarming, and no late toxic effects have so far been observed. Additional studies are in progress.

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CASE OF STREPTOCOCCUS VIRIDANS PNEUMONIA SUCCESSFULLY TREATED WITH PENICILLIN

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The introduction of new remedies is ordinarily followed by numerous articles dealing with their clinical application, and until sufficient data have been collected, critical reports of individual cases are of value. This is particularly true when the subject is a rare disease with a high mortality rate, since it is unlikely that any one investigator would have the opportunity to treat a large number of cases. The present report concerns a patient who suffered from pneumonia due to *Streptococcus viridans* (*S. alpha*). He was critically ill and had consolidation of both lower lobes. After an unsuccessful trial of therapy with sulfadiazine, penicillin was employed, and the patient made a complete recovery.

Pneumonia due to *S. viridans* is an uncommon disease, and one which is even less commonly diagnosed. It is most often confused with primary atypical (viroid) pneumonia of undetermined or of virus origin. It is characterized usually by a prolonged severe course with a high mortality rate. Four of the 5 cases reported in a previous article[1] died. The lesion is usually lobar with a tendency to spread to involve more than 1 lobe. A prominent symptom is severe pleural pain. The sputum is thick and mucoid or mucopurulent. The "prune-juice" sputum seen in pneumococcic pneumonia is never observed, and bloody sputum is rare. Leukocytosis may or may not be present. Bacteremia is quite common but does not affect the prognosis. The usual rapid method of sputum typing by the capsule-swelling phenomenon will fail to disclose the *S. viridans*. Sputum culture on blood agar plates is essential for its isolation. Mouse inoculation followed by plating of the peritoneal exudate of the mouse is also a satisfactory method. The bile solubility test should be performed to differentiate pneumococcic from streptococcic colonies, since only the former are bile-soluble. In the cases previously described,[1] the *S. viridans* was cultured from the blood or the chest fluid as well as the sputum. In the present instance the blood was sterile, and no pleural exudate was noted. However, the clinical picture taken in conjunction with the finding of *S. viridans* in the sputum in pure culture on several occasions, was sufficiently convincing to warrant the diagnosis of *S. viridans* pneumonia.

The failure to respond to sulfonamides corresponds with our previous experience with this disease. It is interesting to note that the response of the fever to penicillin was not immediate, though the general condition improved in 24 hours. The temperature fell by lysis 4 days after this treatment was started. This gradual response to treatment has been reported in pneumonia and other conditions treated with penicillin. The positive results in this case agree with the *in vitro* activity of penicillin against the *S. viridans* reported by Dawson and Hobby.[2]

Spread of the pneumonia to involve a fresh lobe during the course of therapy was noted in this case, though it seems likely that this new process was already under way when treatment with penicillin was initiated. The only untoward reactions were a chill soon after the administration of the initial (intravenous) dose of penicillin, and an urticarial rash which appeared after 7 days of treatment.

The following is the abstract of the case giving the details of the clinical course and the therapy:

Case Abstract. A 31 year old medical officer was admitted to a general hospital on Oct. 9, 1943. His illness began on Oct. 5 with fever, cough and general malaise. He continued at work until Oct. 8 when he noticed occasional chills, and his temperature rose to 102.4° F.

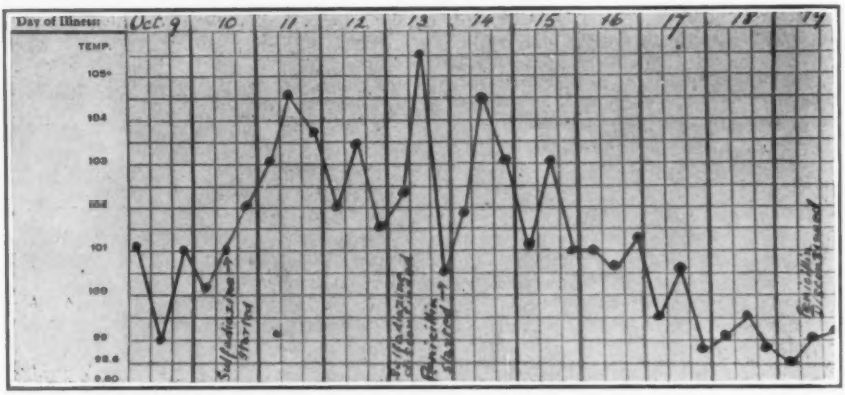

FIG. 1.—Patient's temperature chart for Oct. 9 to 19.

On admission the temperature was 101° F. (see Fig. 1), and the pharynx was mildly injected. The lungs were normal. The rest of the examination was negative. The admission diagnosis was upper respiratory infection. The white blood cells numbered 5500 (57% neutrophils, 36% lymphocytes, 4% monocytes, 2% eosinophils and 1% basophils). The sputum was gray-brown, mucopurulent, and showed numerous pus cells and gram-positive cocci in chains. No pneumococci were found. Culture on blood-agar plates showed *Streptococcus viridans* in pure culture. The organisms were not bile-soluble. A mouse was inoculated with the sputum and survived. Roentgen ray of the chest taken on Oct. 9 was negative. On Oct. 10 the patient had pleuritic pain in the right chest and there was diminished resonance and diminished breath sounds at the right base. Roentgen ray (Fig. 2) showed a patchy infiltration at the right base. Sulfadiazine therapy was started on Oct. 10, the patient receiving 2 gm. orally at 1 P.M. and 1 gm. every 4 hours thereafter. Despite the fact that adequate blood levels were obtained (8 to 9 mg. per 100 cc.), the patient did not respond well. The temperature remained between 103° and 104° F. He was dyspneic and complained of severe pleuritic pain on the right side. He was placed in an oxygen tent on Oct. 11. By this time the classic signs of consolidation in the right lower lobe were present, namely dulness, bronchial breathing and a few râles. The sputum was thick, green and mucopurulent. Culture on blood agar again revealed *S. viridans*. Several samples of the sputum showed no tubercle bacilli. Blood cultures were sterile. The white count on Oct. 13 was 5800 (72% neutrophils, 27% lymphocytes, 1% eosinophils). Another mouse was inoculated intraperitone-

ally with the sputum, and examination of the peritoneal exudate showed *S. viridans* in pure culture. The organisms, as before, were not bile-soluble. Sputum culture on Oct. 15 showed *S. viridans* as the predominant organism with a few colonies of *Staph. albus*. A Roentgen ray taken on Oct. 13 (Fig. 3) showed increased consolidation at the right base. There were physical and roentgenologic signs of congestion at the left base as well.

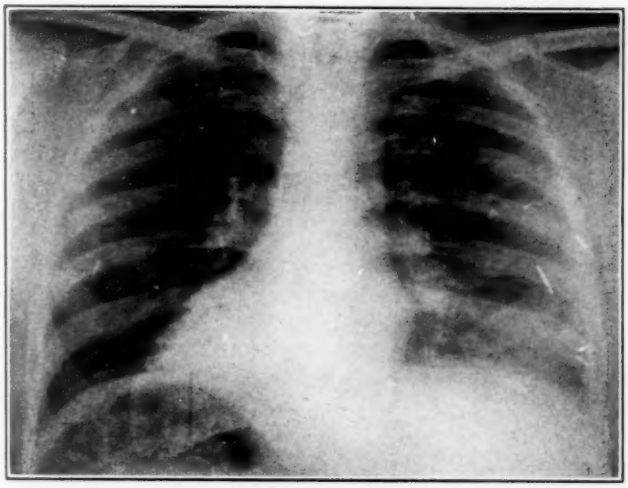

FIG. 2.—Roentgenogram Oct. 10 showing patchy infiltration of right base.

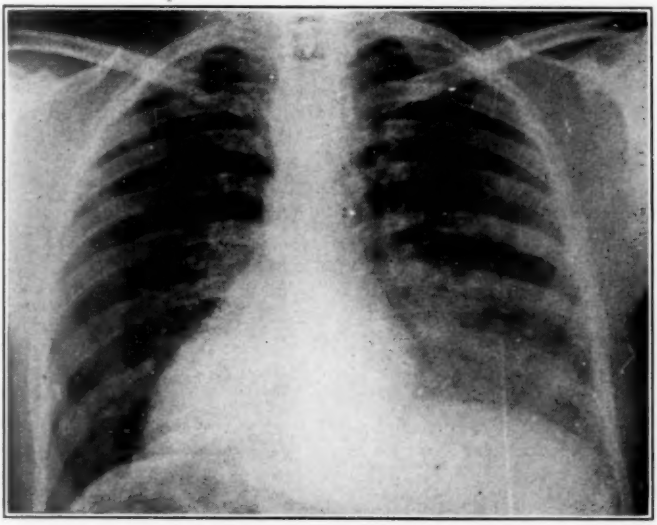

FIG. 3.—Roentgenogram Oct. 13 showing increase in consolidation of right lower lobe and early involvement of left lower lobe.

In view of the fact that the patient did not show any improvement after 72 hours of chemotherapy, sulfadiazine was discontinued and penicillin therapy

was begun. On Oct. 13 he was given 25,000 units of the drug intravenously and 25,000 units intramuscularly. There was no immediate reaction but about 30 min. later he had a severe chill and sinus tachycardia which subsided

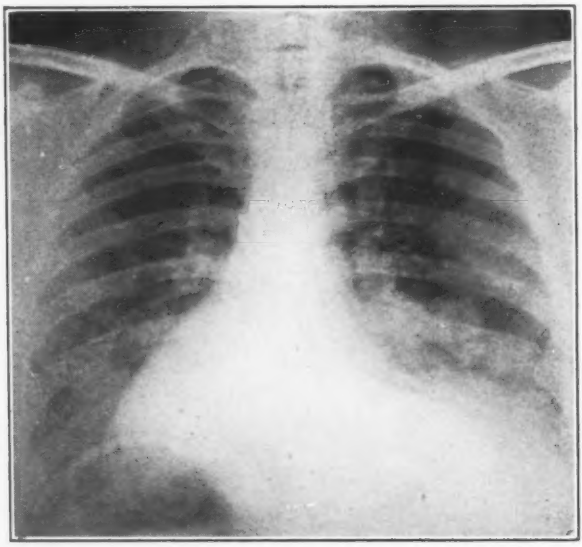

FIG. 4.—Roentgenogram of Oct. 16 demonstrating consolidation of both lower lobes.

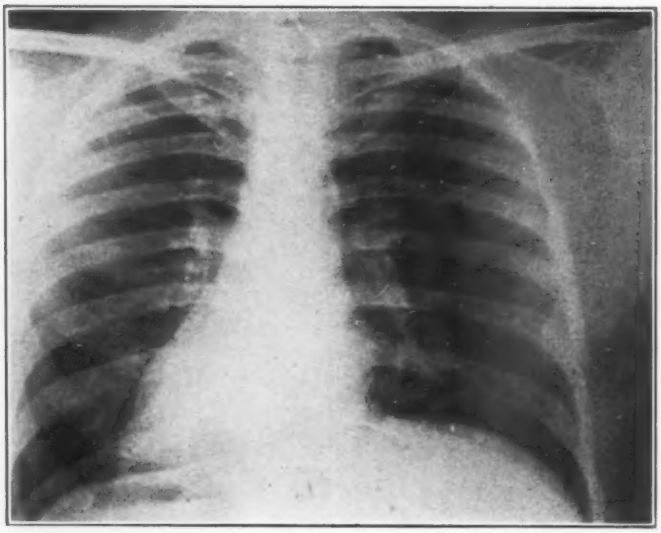

FIG. 5.—Roentgen ray Nov. 6. The pneumonia has resolved completely.

following the use of adrenalin and external heat. Thereafter the dosage of penicillin was 15,000 units dissolved in 3 cc. of distilled water given intramuscularly every 3 hours, 8 times a day. This was continued until Oct. 18.

The patient received a total of 690,000 units intramuscularly and 25,000 units intravenously. The response was gradual, the temperature coming down by lysis by Oct. 18 (see Fig. 1). There were no untoward reactions to the penicillin except that on Oct. 19 it was noted that he had an itchy urticarial rash on the face and neck which disappeared in 24 hours. Although the temperature was only slightly elevated, the patient nevertheless felt exhausted, had severe chest pain and cough. It was noted on Oct. 16 that there were signs of consolidation in the left lower lobe. This was confirmed by Roentgen ray (Fig. 4). A blood count on Oct. 19 showed 12,000 white blood cells (73% neutrophils, 24% lymphocytes, 3% monocytes). On Oct. 20 culture of the sputum still showed *S. viridans* as the predominant organism, with a few colonies of *Staph. albus*. The patient made a slow but uneventful convalescence. Roentgen ray on Nov. 6 (Fig. 5) showed complete clearing of the lesion. After a fortnight's sick leave he returned to full duty.

Summary. This report concerns a case of *S. viridans* pneumonia, an uncommon disease with a high mortality rate, which does not respond to sulfonamides. The patient was treated unsuccessfully with sulfadiazine for 72 hours, following which penicillin was employed. He responded well and made a complete recovery. It is essential for the diagnosis of cases of this sort to culture the sputum of atypical pneumonias on blood agar plates. Once the diagnosis has been made, it is my experience that sulfonamides are not effective. Penicillin appears to be deserving of further trial.

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OBSERVATIONS ON THE CONTINUOUS INTRAMUSCULAR METHOD OF ADMINISTERING PENICILLIN*

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Penicillin is now recognized as being highly efficacious in a variety of infections. The problem of how best to administer it, however, remains unsettled. When it is given orally or by rectal instillation, only very minimal amounts enter the blood stream. Repeated intravenous, intramuscular, or subcutaneous injections have been used. When penicillin is injected into the vein, a high blood concentration is immediately attained but, due to the rapid elimination of penicillin by the kidneys, the level in the blood drops rapidly, usually being below detectable levels in less than 2 hours, as shown by Rammelkamp and Keefer.[10] The same authors found that after subcutaneous

* We wish to thank Miss C. Barbara O'Neil and Miss Ruth L. Mayer for technical assistance.

injection absorption was slow and irregular. Fleming,[3] and also Cooke and Goldring,[1] have recently stated that absorption from a subcutaneous site compares favorably with that following intramuscular injections. This method has not yet had wide trial. Furthermore, concentrated solutions of penicillin may be irritating when given subcutaneously. The method of intermittent injections at intervals of 2, 3, or 4 hours is the most widely used method at the present time, because by this route penicillin can be given simply and fairly adequate blood concentrations can be attained.

When high blood concentrations are required intravenous instillation by means of a "continuous drip" apparatus has been used very successfully. Herrell[5] stated that one-half the amount of penicillin is required to maintain the same serum level by this method as by repeated intramuscular injections. This method, however, requires that the patient possess suitable veins, necessitates immobilization of the patient and frequently results in phlebothrombosis. Rantz and Kirby[11] on administering penicillin subcutaneously obtained plasma levels about 50% as high as by intravenous administration. Others[5] have found this method of administration irregular, variable and uncertain. For these reasons, when the method of constant intramuscular administration was advocated by Harris,[4] by Morgan and his associates[7] and others[6] we began to use it immediately, and up to the present time have employed it in 110 patients. Because this method has worked so well in our hands we are reporting the concentrations of penicillin attained in the blood of the patients we have studied in comparison with those achieved by other methods.

Material and Methods. The patients studied were under treatment for a variety of infections. Although some of the blood specimens were obtained during febrile periods and others when there was no fever, we have found no correlation between the patient's temperature and the absorption of penicillin, and have accordingly made no differentiation in this regard. Our procedure has been to calculate the amount of sodium penicillin required for each 12-hour period and to dissolve this in 500 or 1000 cc. of isotonic salt solution. This was placed in the flask connected with a Murphy drip apparatus to which a 2-inch, 18 or 20 gauge needle was attached. The needle was inserted into the lateral aspect of the thigh or into the gluteal muscles and the solution allowed to flow in at a constant rate over the course of 12 hours. When 1000 cc. of solution were used for a 12-hour period, the proper rate of flow was usually 30 ot 40 drops per minute. At the end of the 12-hour period the flask was refilled with freshly made penicillin solution. If a point was reached where the fluid was not being absorbed from the muscles, the needle was changed to the other extremity or from the thigh to the buttocks or *vice versa*. Usually the whole setup was changed at the time the needle was reinserted. Such changes were never required more often than every 24 hours, and frequently were not necessary for intervals of 48 or 96 hours. Twenty-five cubic centimeters of 1% procaine were added to each liter of solution when necessary to relieve pain and discomfort. Constant intravenous administration, when used, was also given by use of the Murphy drip apparatus.

Penicillin administered by intermittent intramuscular injection was dissolved so that each cc. of saline contained 10,000 units of penicillin. The injections were made into the deltoid, thigh or gluteal muscles using a $2\frac{1}{2}$-inch, 18 or 20 gauge needle. There was no apparent difference in blood levels regardless of the site of injection. The length of the needle was important, no

penicillin being detectable in the blood stream in the case of one patient when a 1-inch, 26 gauge needle was used for the injection.

Blood serum was obtained from the patients treated by the continuous method at intervals during the period of administration, and for 2 hours after treatment was stopped. From the patients receiving multiple individual injections, blood specimens for penicillin determination were obtained at hourly intervals following three consecutive injections and also at other scattered intervals. Penicillin determinations were done by the method of Rammelkamp.[9]

Results. Table 1 shows the blood concentrations attained in patients treated by means of the "intramuscular drip" method, when 100,000 units were given during a 12-hour period. The levels remained fairly constant after the first hour, varying in most instances from 0.078 to 0.312 Oxford units per cc. Occasionally the concentration went as high as 2.5 and as low as 0.0195 units per cc. It will be noted that the method was varied in several different ways. In some patients the injections were given in the thigh muscles, and in others in the glutei. The 24-hour dose of penicillin was dissolved in 1000 cc. of isotonic salt solution in some instances, and in 2000 cc. in others. In some cases, neosynephrin was administered along with the penicillin. No appreciable differences were observed in the blood penicillin concentrations as a result of any of these procedures. The addition of 25 cc. of 1% procaine to each liter of solution to relieve pain and discomfort likewise caused no alteration in blood levels.

Table 2 shows the frequency with which various blood concentrations were achieved by the continuous intramuscular injection of 200,000 units over a 24-hour period as compared with those attained at varying intervals after single intramuscular injections. It is obvious that administration of penicillin by a series of single injections will not maintain levels as high as when the drug is given by continuous injection. When injections of 25,000 units every 3 hours or 20,000 units every 2 hours were given, (200,000 to 240,000 units for a 24-hour period), the median blood penicillin concentration 1 hour after each injection, was not as high as was the continuous level when only 200,000 units were given over a 24-hour period by the continuous method. The blood penicillin levels 2 and 3 hours after a single injection were considerably lower, and often the amount of penicillin present was undetectable by the method used. A concentration of 0.039 units of penicillin per cc. has proved efficacious against most infections susceptible to penicillin.[10] Using this level as a criterion, we found that in 3 patients who were given 25,000 units of penicillin by intramuscular injection every 3 hours, an adequate concentration of penicillin was present in 16, or 80% of 20 determinations. In 9 patients who were given 20,000 units every 2 hours, a level of 0.039 units per cc. or above was found in 51 (67%) of 76 determinations. Following the administration of 15,000 units of penicillin every 2 hours, this same level was obtained in only 29, (63%), out of 46 determinations. There were 25 patients who received 200,000 units of penicillin by continuous intramuscular injections. When the blood was examined at various intervals during the 24-hour period, these therapeutically effective levels were achieved in 142 (96%) of 152 determinations.

TABLE 1.—SERUM PENICILLIN CONCENTRATIONS OBTAINED IN PATIENTS RECEIVING PENICILLIN BY THE CONTINUOUS INTRAMUSCULAR METHOD
(200,000 Units of Penicillin Administered in 24 Hours)

Patient	Site of administration	Amount of isotonic saline solution (cc.)	Serum penicillin concentration								
			1 hr.	3 hrs.	6 hrs.	9 hrs.	12 hrs.	18 hrs.	24 hrs.	25 hrs.	26 hrs.
S. T.	Thigh	2000	.039	.078	.078	.078	.078	.156	.156	.039	.0195
K. D.	Thigh	2000	.078	.078	.156	.078	.078	.078	.039	0	0
C. P.	Thigh	2000	.0195	.156	.156	.625	.156	.156	2.5	.039	.0195
R. W.	Thigh	2000	.312	.156	.156	.312	.312	.156	.156	.0195	0
L. P.	Thigh	2000	.156	.312	.156	.312	.312	.312	.156	.039	.0195
W. G.	Thigh	2000	.312	.078	.156	.156	.312	.625	.625	.156	.039
N. B.	Thigh	2000	.078	.078	.078	.156	.156	.078	.078	.0195	0
J. G.	Thigh	2000	.039	.078	.156	.156	.625	.625	.625	.0195	0
L. W.	Thigh	2000	.0195	.078	.156	.156	.156	.156	.156	.039	0
C. P.	Thigh	2000	.039	.156	.156	.312	.312	.156	.156	.039	.0195
L. P.	Thigh	1000	.078	.156	.078	.078	.078	.156	.078	.0195	0
S. T.	Thigh	1000	.039	.078	.078	.078	.078	.078	.156	.031	0
L. D.	Buttock	2000	.078	.078	.078	.078	.078	.156	.156	.039	.0195
W. B.	Buttock	2000	.039	.039	.039	.078	.078	.078	.156	.0195	0
J. C.	Thigh	2000*	.039	.039	.039	.039	.039	.078	.078	.0195	0
C. F.	Thigh	2000[a]	.078	.078	.039	.039	.156	.156	.156	.078	.0195
J. M.	Thigh	2000[a]	.0195	.039	.0195	.078	.078	.078	.078	.039	.0195
C. S.	Thigh	2000[b]	.078	.156	.156	.156	.156	.078	.0195	0	0
C. J.†	Thigh	1000	.625	.625	1.25	1.25	1.25	.039‡	0§		
V. G.†	Thigh	1000	1.25	2.5	2.5	2.5	2.5	.039‡	0§		

* 4 cc. of 1% neosynephrin added. [a] 10 cc. of 1% neosynephrin added. [b] 20 cc. of 1% neosynephrin added.
† 100,000 units of penicillin administered in 12 hours.
‡ 13-hour level.
§ 14-hour level.

TABLE 2.—COMPARISON OF PENICILLIN CONCENTRATIONS OBTAINED IN THE BLOOD SERUM FOLLOWING INTERMITTENT AND CONTINUOUS INTRAMUSCULAR ADMINISTRATION

Penicillin levels (units per cc.)	25,000 units every 3 hrs.			20,000 units every 2 hrs.		15,000 units every 2 hrs.		200,000 units penicillin in 1000 cc. and 2000 cc. isotonic saline in 24 hours* by constant intramuscular administration										
	1 hr.	2 hrs.	3 hrs.	1 hr.	2 hrs.	1 hr.	2 hrs.	1 hr.	3 hrs.	6 hrs.	9 hrs.	12 hrs.	18 hrs.	24 hrs.	Other hours	All determinations 3 to 24 hrs. inclusive	1 hr. after termination of drip	2 hrs. after termination of drip
2.5	0	0	0	0	0	0	0	0	1	1	1	1	0	1	0	4	0	0
1.25	0	0	0	0	0	1	0	1	0	1	1	1	0	0	0	3	0	0
.625	1	0	0	1	0	1	0	1	1	0	1	1	2	2	0	7	0	0
.312	3	0	0	3	0	0	0	2	1	0	3	4	1	0	3	12	0	0
.156	1	2	1	13	2	7	0	1	5	9	5	5	8	9	1	42	1	0
.078	1	1	2	17	5	11	1	6	9	5	7	7	7	4	3	42	2	0
.039	0	2	2	7	3	2	6	6	4	4	3	2	0	2	0	15	10	1
.0195	0	1	3	0	6	1	5	4	0	1	0	0	1	1	3	6	6	7
.009	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
None	0	0	0	0	19	0	11	0	0	0	0	0	0	0	0	0	2	12
No. of determinations	20			76		46		152										
No. of patients	3			9		7		25										

* Two cases received 100,000 units of penicillin in 1000 cc. isotonic saline in 12 hours.

Figure 1 compares the median concentrations in the serum of patients receiving 200,000 units of penicillin in 24 hours by the continuous intramuscular drip with those receiving 20,000 units every 2 hours by repeated intramuscular injection (or 240,000 units in a 24-hour period). For patients receiving the continuous intramuscular drip, the median serum concentration rose to 0.078 units per cc. at the end of 1 hour. It remained at this level for the next 2 hours, rising to a level of 0.156

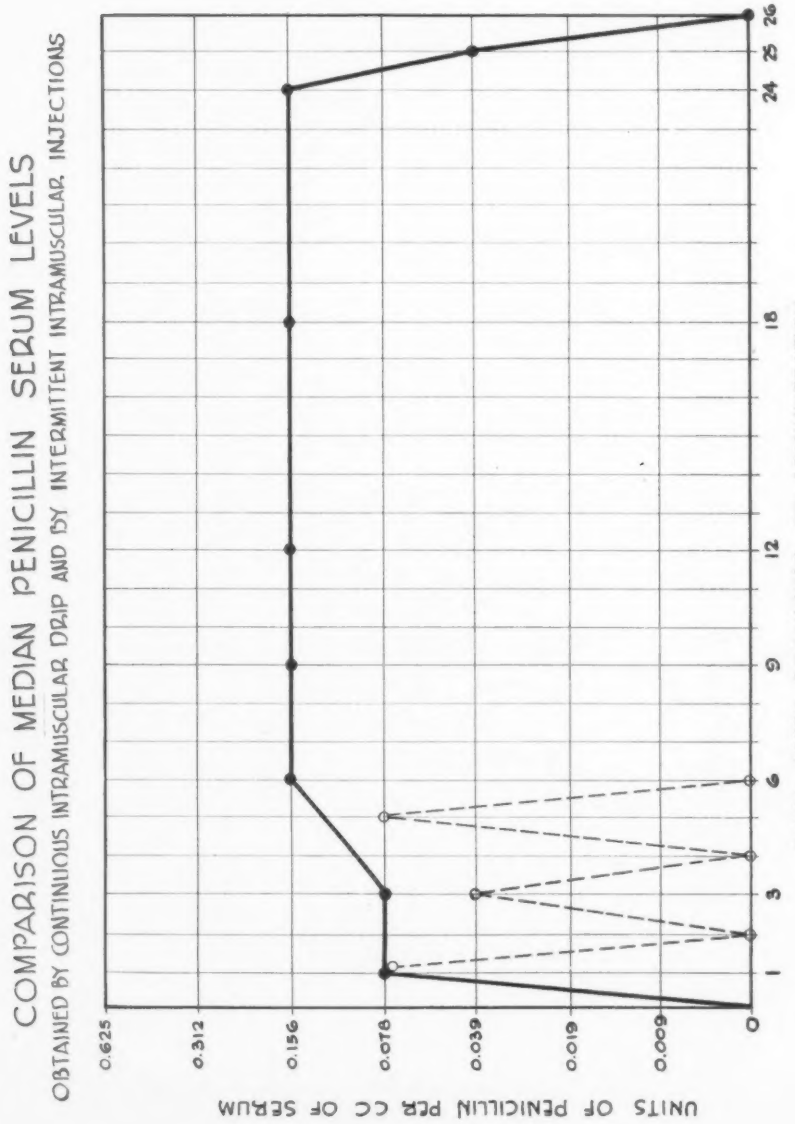

FIG. 1

units per cc. for the remainder of the 24-hour period. The serum level fell to zero within 2 hours after administration was discontinued. This is in marked contrast to the fluctuating median serum levels obtained with doses of 20,000 units every 2 hours. With this method the levels fell from 0.039 or 0.078 units per cc. at the end of 1 hour to zero at the end of 2 hours. The concentrations were determined over a consecutive 6-hour period.

Among the 110 patients to whom we have administered penicillin by the continuous intramuscular method, only 6 complained of mild or moderate discomfort. In 2 of these subjects the pain did not appear until they had received penicillin in one site for several days. When pain at the site of administration did occur, 25 cc. of 1% procaine hydrochloride was added to each liter of solution. This produced prompt and complete relief, so that we were able to continue penicillin administration at the same site as long as treatment was needed, even if this required several additional days. When we added procaine to a penicillin solution *in vitro*, we found that the procaine did not affect the antibacterial activity of the penicillin. Furthermore, the antibacterial activity of serum from patients receiving penicillin together with procaine was no different from the activity of serum from patients receiving penicillin alone.

Discussion. We are of the opinion that continuous intramuscular injection is the method of choice for the parenteral administration of penicillin. In a series of 110 cases, we have observed no deleterious effects, except for moderate pain and tenderness at the site of injection in 6 patients. Twenty-five cubic centimeters of 1% procaine added to the solution afforded relief from these discomforts. McAdam and his associates[6] and others[8,12] obviate this difficulty by using only 100 to 600 cc. in a 24-hour period, employing a special apparatus for the administration of these small volumes.

We have found that when the 24-hour dose of penicillin is given in 2 liters of fluid, continuous observation is not necessary in order to insure an even rate of flow, and that pain at the site of injection seldom occurs, especially if the needle is changed to another site every 24 to 96 hours. Thighs and buttocks are both available for these shifts, since we have found that there is no difference in the concentration of penicillin in the serum administered in either of these sites. When a patient does develop pain at the site of injection, the simplest procedure is to add procaine to the solution being administered. This relieves the pain and does not affect the activity of the penicillin.

The obvious advantages of continuous over intermittent intramuscular administration are the achievement of higher continuous serum levels and the elimination of the pain of repeated injections. We have shown that when 8333 units of penicillin are given per hour by the continuous intramuscular method, 96% of the blood penicillin concentrations were therapeutically effective, whereas with intramuscular injections of 25,000 units every 3 hours, only 80% of the concentrations obtained were therapeutically effective. The corresponding figures for the injection of 20,000 and 15,000 units every

● CONTINUOUS INTRAMUSCULAR DRIP USING 200,000 UNITS PENICILLIN IN 2 LITERS
○ INTERMITTENT INTRAMUSCULAR INJECTION USING 20,000 UNITS PENICILLIN EVERY TWO HOURS

FIG. 1

2 hours are 67 and 63% respectively. McAdam made similar observations expressing his results slightly differently. He[6] has shown that 6 times as much penicillin is required to maintain a bactericidal level when the drug is given at intervals of 4 hours than when it is given by continuous intramuscular administration; 3 times as much penicillin is required when the interval is 3 hours; and at least $1\frac{1}{4}$ times as much when the interval is 2 hours. Much nursing time is saved by eliminating the necessity of preparing each penicillin injection. The patient can be allowed almost complete freedom, including bathroom privileges, while receiving the continuous intramuscular drip.

When compared to continuous intravenous administration, the continuous intramuscular method appears superior, obviating the need for good veins, eliminating trauma to the veins and the occurrence of phlebothrombosis. In our hands, similar concentrations in the blood serum were obtained by the continuous intramuscular method when only one-half as much penicillin was used as in the continuous intravenous method. Dawson and Hunter[2] have obtained higher serum levels with the continuous intramuscular than with the continuous intravenous method of administration of the drug.

Summary and Conclusions. 1. When penicillin is administered at the rate of 200,000 units in 24 hours (8333 units per hour) by the continuous intramuscular method, the concentration of penicillin in the blood remains constant and at therapeutically effective levels 96% of the time; whereas, with injections of 25,000 units every 3 hours, similar concentrations are obtained only 80% of the time. The corresponding figures for the injection of 20,000 and 15,000 units every 2 hours are 67 and 63%, respectively.

2. There were no deleterious effects or complications in a series of 110 patients in whom this method was employed, except for mild to moderate pain or discomfort at the site of injection in 6 patients. Pain was usually prevented by changing the location of the needle every 24 to 96 hours. When it did occur, it was relieved promptly and completely by the addition of procaine to the penicillin solution.

3. With this method, repeated painful intramuscular or intravenous injections are avoided. The veins of the body are not traumatized and phlebothrombosis is eliminated. The patient has almost complete freedom of activity.

4. The continuous intramuscular drip method is the method of choice for the administration of penicillin to very ill patients who require continuously high concentrations of the drug in the blood.

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ELECTROCARDIOGRAPHIC OBSERVATIONS IN NORMAL THYROIDECTOMIZED AND THIOUREA TREATED RATS*

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With the Technical Assistance of Mr. Albert H. Stenger

The literature on the use of the electrocardiograph on small laboratory animals, such as mice and rats, is extremely sparse.

Agduhr and Stenström[1] investigated electrocardiographic changes in mice after cod-liver oil treatment. A string galvanometer built for human use with a string speed of 0.01 second was used in this work. Small zinc plates, amalgamated with mercury and wrapped in cotton soaked in physiologic NaCl solution were used as electrodes. The standardization was 1 mv. per centimeter. An attempt was made to establish the normal mouse electrocardiogram using a small number of animals. The average heart rate was found to be 560 per minute with a conduction time varying between 0.025 and 0.045 second. The authors also stated that arrhythmias and extremely low deflections in Lead 1 were commonly found, and that there were changes in the electrical axis of the same animal on repeated examinations.

The most characteristic statement concerning the findings of Agduhr and Stenström, indicating the inadequacy of the apparatus used, is, "A feature generally met with in the electrocardiograph of mice is that the summits of the T waves can almost never be discovered, which seems noteworthy inasmuch as the other deflections are sometimes nearly as large as those of the human electrocardiogram. Instead of an independent T summit, there appears however, with great

* This report contains material accepted in partial fulfilment of the requirements for the degree of Master of Science, New York University.

consistency, terminating the QRS complex, a slow return of the string to the isoelectric line . . . ."

Weiss, Haynes, and Zoll[11] studied electrocardiographic changes in vitamin deficient rats and in 7 normal rats. The main deflections were found to be upright in all leads with extremely low deflections in Lead 1. The average voltage of the main deflection in Lead 2 (R_2) was stated to vary between 0.8 and 0.2 mv. The average height of T_2 ranged from 0.25 to 0.05 mv. The statement characteristic of the inadequacy of the galvanometer used in this investigation is, that the origin of all T waves was found to be elevated. This fact is also amply illustrated by graphs shown by the authors.

Griffith[5] in his textbook simply stated that electrocardiograms can be taken in rats by means of a string galvanometer and needle electrodes, and showed a graph of Lead 2.

Rappaport and Rappaport[10] pointed out for the first time, the complete inability of string galvanometers alone, and also commercial amplifier electrocardiographs, to register correctly the electrocardiographic pattern of any animal with a heart rate essentially higher than that of man. The slow string speed or the high inertia of the mirror galvanometer used causes superimposition of deflections with consequent graphic distortion. In order to overcome these difficulties, the authors recommended the use of a resistance coupled amplifier in conjunction with a string galvanometer with high vibration speed.

The primary purposes of this investigation are to establish, with the use of this recently recommended equipment, first, an average pattern of an electrocardiogram for the normal rat; and secondly, to study such electrocardiographic changes which may be produced by thyroidectomy and compare them with changes following treatment with thiourea.

Material and Methods. In order to establish an average electrocardiographic pattern, 24 male and 26 female hooded albino rats were used. Their weights ranged from 107 to 360 gm. Out of these 50 rats, 8 were thyroidectomized and 8 were subjected to 1% thiourea in drinking water. The electrocardiograms of the thyroidectomized animals were repeated after 1 month, as were those of the thiourea treated animals after 3 weeks. Also used in this study were 2 male rats which had been thyroidectomized 6 months previously.*

For the purpose of electrocardiography, all animals were anesthetized with intraperitoneal injections of 30 mg. of nembutal per kg. of body weight, and subsequently permitted to rest for at least 15 minutes. The recording instrument used was a commercial string galvanometer electrocardiograph together with the electronic amplifier (Fig. 1) recommended by Rappaport and Rappaport.[10]†

Because of alternating current interference it was necessary to place the animal into a wire cage, grounded together with amplifier and galvanometer. To reduce interference further, a 0.1 mfd condenser was placed into the main ground wire through which the three parts of the apparatus were then grounded. The 3 lead wires of the amplifier were then connected to the animal by thrusting 26-gauge hypodermic needles attached to these wires, beneath the skin of the left and right foreleg and left hindleg for a distance of 1 cm. In order

* Supplied by Dr. A. S. Gordon.

† Acknowledgment with thanks is hereby made to the Flushing Hospital for use of the electrocardiograph.

to reduce further any disturbing AC interference, it was essential to rub the fur of the legs with electrode jelly before applying the electrodes. Through this procedure, the electrode-skin resistance was reduced, thereby eliminating another possible pick-up of extraneous currents.

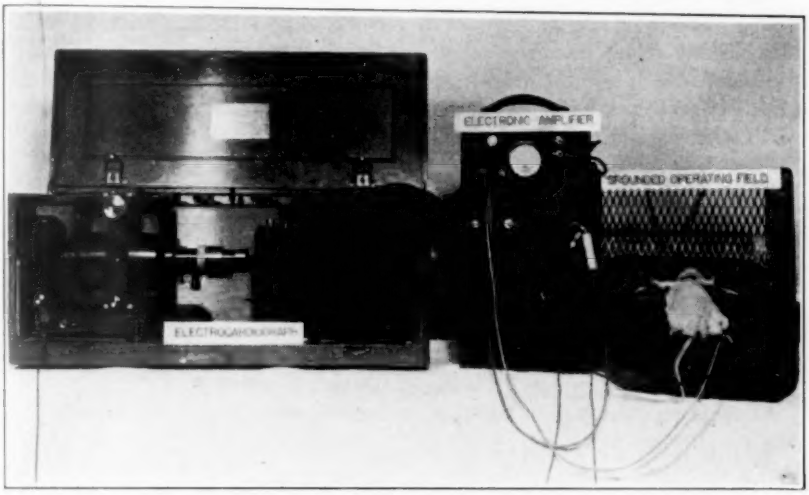

FIG. 1.—Electrocardiograph with electronic amplifier in position for use.

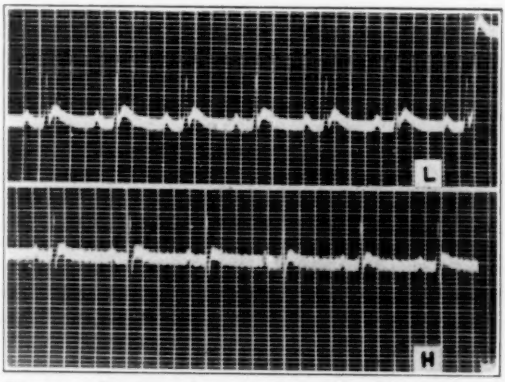

FIG. 2.—Electrocardiogram taken with low (L) and high (H) string speeds respectively (Lead 2).

The standardization used in this investigation was 20 mm. per millivolt. The recording speed was 75 mm. per second, *i. e.*, 3 times normal speed.

In order to demonstrate the difference in appearance in a rat electrocardiogram taken with low and high string speed, Figure 2 is shown.

Both graphs were taken in Lead 2 position on the same animal. The upper one was recorded by means of a commercial string galvanometer electrocardiograph. This graph shows clearly the superimposition of the T waves upon the terminal part of the QRS complexes. The take-off of the T waves is markedly elevated. S waves are minimal. The lower graph, taken with the same instrument but in conjunction with the amplifier and high string tension,

shows the take-off of the ST segments to be in the isoelectric line and the presence of a well formed S wave. The increase of deformities with increased heart rate was well demonstrated by the graphs of white mice shown in the publication of Rappaport and Rappaport.[10]

Experimental Results. A. *Analysis of Electrocardiograms on Normal Rats.* The average pattern of a normal rat electrocardiogram was established from calculations of 50 graphs taken on 50 individual animals. Because the amplitude of the QRS complexes in Leads 1 and 3 is greatly affected by changes of the electrical axis and because of Einthoven's law, only amplitudes of the waves in Lead 2 were used for the detection of electrocardiographic changes.

The mean measurements of the different components with their deviations from the mean and their range is shown in Table 1.

TABLE 1.—MEASUREMENTS OF COMPONENTS OF THE ELECTROCARDIOGRAPHIC COMPLEX IN 50 ANIMALS

	Mean	Range
Weight of animals	189 gm. ± 53	360–107
Heart rate	328 ± 17 per min.	360–261
P–R interval (conduction time)	0.047 sec. ± 0.002	0.053–0.038
Height of R_2 waves	0.463 mv. ± 0.097	0.750–0.300
Height of T_2 waves	0.106 mv. ± 0.029	0.225–0.050

In this table a remarkably wide range of measurements can be seen, which however, is thoroughly comparable to the wide range of normal values observed in humans. The sexes were equally distributed in this series and no sex linked variations could be observed throughout the study.

The distribution of axis deviation in this series is shown in Table 2.

TABLE 2.—DISTRIBUTION OF AXIS DEVIATION

Axis deviation	No. of rats
Left	8
Tendency to left	6
None	27
Tendency to right	9
Right	0

Thus, slightly more than half of the animals showed no axis deviation at all; approximately 28% showed deviation to the left; and only 18% showed a tendency to right axis deviation. Frank right axis deviation was never observed.

In order to determine the influence of animal weight upon axis deviation, Table 3 was drawn up.

TABLE 3.—AXIS DEVIATION ACCORDING TO WEIGHT OF RAT

Animal weight (gm.)	Left	Tendency to left	None	Tendency to right	Right
100–150	1	1	7	6	0
151–200	5	2	8	2	0
201–250	3	0	5	1	0
251–300	1	0	4	0	0
301–360	1	0	3	0	0

This table shows the preponderance of "tendency to right" over "tendency to left" in the lower weight group, which diminishes and finally disappears completely in the higher weight groups.

These results are not dissimilar to those reported by Weiss *et al.*,[11] although in this series, all waves are somewhat lower because of lack of superimposition of deflections. The general outline of the complexes is identical with those of the human electrocardiogram. The deflections in Lead 1 were found to be very low in the majority of animals, a phenomenon which can easily be explained by the relative center position of the rat heart in the first lead, and by the relative shortness of this lead as compared to the remainder of the standard leads. Deflections of Lead 3 were found to be usually well formed but somewhat lower than those seen in Lead 2. All ST segments were found to be isoelectric and not elevated as shown by other authors. Well formed S waves were found in the majority of Leads 2 and 3.

B. *Analysis of Electrocardiograms on Thyroidectomized Animals.* The electrocardiographic effects of thyroidectomy of 4 weeks standing are shown in Table 4. All animals were thyroidectomized immediately after the first electrocardiogram and rechecked after 1 month. Also included in this table are 2 rats with thyroidectomies of 6 months standing. Attention should be called to the fact that Rat 6 was only hemi-thyroidectomized because of excessive bleeding.

In order to avoid any misinterpretation of changes in the amplitude of R waves which could be accounted for by the absence or occurrence of a prominent S wave, the total amplitude of the QRS complex was measured and tabulated in millimeters. Although it is customary to express all amplitudes in millivolts, this was avoided in this instance, because R waves are positive in direction whereas S waves are negative. Their algebraic sum is therefore less indicative of any change than their geometric sum (R+S).

TABLE 4.—EFFECTS OF THYROIDECTOMY

Sex and animal No.	Time since thyr.x.	Wt.	Heart rate per m.	P–R interval (sec.)	R_2 (mv.)	Total amplitude R + S (mm.) (Lead 2)	T_2 (mv.)	Axis deviation
♀ 1	0	139	355	0.045	0.750	19.0	0.113	Tend. rt.
1 R*	1 mo.	185	344	0.046	0.500	14.0	0.075	Tend. rt.
♂ 2	0	137	351	0.038	0.675	15.0	0.125	None
2 R	1 mo.	170	336	0.042	0.500	14.0	0.100	Tend. rt.
♂ 4	0	140	348	0.043	0.388	16.0	0.175	Tend. rt.
4 R	1 mo.	185	324	0.054	0.350	13.5	0.055	Tend. lt.
♂ 6	0	125	324	0.048	0.445	12.5	Isoel.	Tend. rt.
6 R	1 mo.	128	354	0.049	0.500	12.5	0.063	Tend. lt.
♂ 8	0	171	360	0.044	0.425	12.5	0.163	None
8 R	1 mo.	238	348	0.046	0.325	10.0	0.100	Tend. rt.
♀ 9	0	162	339	0.042	0.750	19.5	0.138	None
9 R	1 mo.	172	330	0.045	0.563	14.5	0.113	Tend. rt.
♀ 10	0	202	357	0.046	0.355	12.0	0.105	Tend. rt.
10 R	1 mo.	248	333	0.048	0.205	9.0	0.025	Tend. lt.
♂ 22	0	163	330	0.047	0.450	13.0	0.088	None
22 R	1 mo.	210	330	0.047	0.388	12.0	0.063	None
♂ 53	6 mos.	327	300	0.050	0.325	12.5	0.100	Tend. lt.
54	6 mos.	271	258	0.064	0.275	7.5	0.063	Tend. rt.

* The letter R after the animal number indicates a repeat electrocardiogram on the same animal after the time interval stated in the second column.

This table shows that in 6 of 7 animals, disregarding Rat 6, there was a small weight gain, a drop in heart rate, and a concomitant widening of the P–R interval. The voltage of the R waves also decreased in these animals as did the total amplitude of the QRS complex (R+S). There was also a definite lowering of all T waves. Although there was a change of axis deviation in the majority of animals, no definite trend toward any direction could be made out. Of the 2 animals thyroidectomized 6 months previously, 1 showed a heart rate somewhat lower, the other a heart rate markedly lower than that observed after 1 month of thyroidectomy. The conduction time of these animals was correspondingly lengthened and all positive waves were found to be lower than their corresponding means.

C. *Analysis of Electrocardiographs on Thiourea Treated Animals.* The electrocardiographic changes effected by the administration of 1% thiourea in drinking water for a period of 3 weeks are compiled in Table 5.

Table 5.—Effects of Thiourea (1% in Drinking Water)

Sex and animal No.	Time of treat.	Wt.	Heart rate per m.	P–R interval (sec.)	R_2 (mv.)	Total amplitude R + S (mm.) (Lead 2)	T_2 (mv.)	Axis deviation
♀ 12	0	107	321	0.048	0.488	16.0	0.200	Tend. rt.
12 R	3 wks.	93	222	0.063	0.575	18.5	0.100	Tend. rt.
♀ 13	0	116	333	0.044	0.513	14.0	0.150	None
13 R	3 wks.	100	279	0.048	0.575	15.0	0.075	Tend. rt.
♂ 14	0	134	327	0.044	0.475	14.0	0.163	None
14 R	3 wks.	102	228	0.059	0.600	17.5	0.075	Tend. rt.
♂ 16	0	158	345	0.046	0.613	16.5	0.088	Tend. lt.
16 R	3 wks.	115	285	0.058	0.650	18.0	0.050	None
♂ 17	0	147	354	0.046	0.538	14.0	0.150	None
17 R	3 wks.	137	210	0.064	0.538	14.0	0.075	Tend. rt.
♀ 18	0	110	261	0.054	0.712	17.0	0.138	Tend. rt.
18 R	3 wks.	102	162	0.064	0.763	18.0	0.050	Tend. rt.
♀ 19	0	113	306	0.046	0.650	18.0	0.025	None
19 R	3 wks.	104	206	0.050	0.550	18.0	Isoel.	Tend. rt.
♀ 20	0	118	345	0.045	0.550	14.5	0.150	None
20 R	3 wks.	85	210	0.059	0.563	16.5	0.100	Tend. rt.

All 8 animals lost weight during the treatment. Their heart rate was reduced to approximately two-thirds of the original value, accompanied by a corresponding lengthening of the conduction time. In striking contrast to the thyroidectomized animals, these animals showed an increase of voltage in R_2, 6 times out of 8. This was borne out by a parallel increase in total QRS amplitude (R+S). The T waves showed a drop of voltage in all cases, much more drastic than that seen in thyroidectomized animals. Six animals out of 8 showed a definite shift of the electrical axis to the right, whereas 2 retained their original axis deviation.

Discussion. In order to demonstrate more clearly the electrocardiographic changes appearing after thyroidectomy, the graphs of representative animals before and after thyroidectomy are shown in Figure 3.

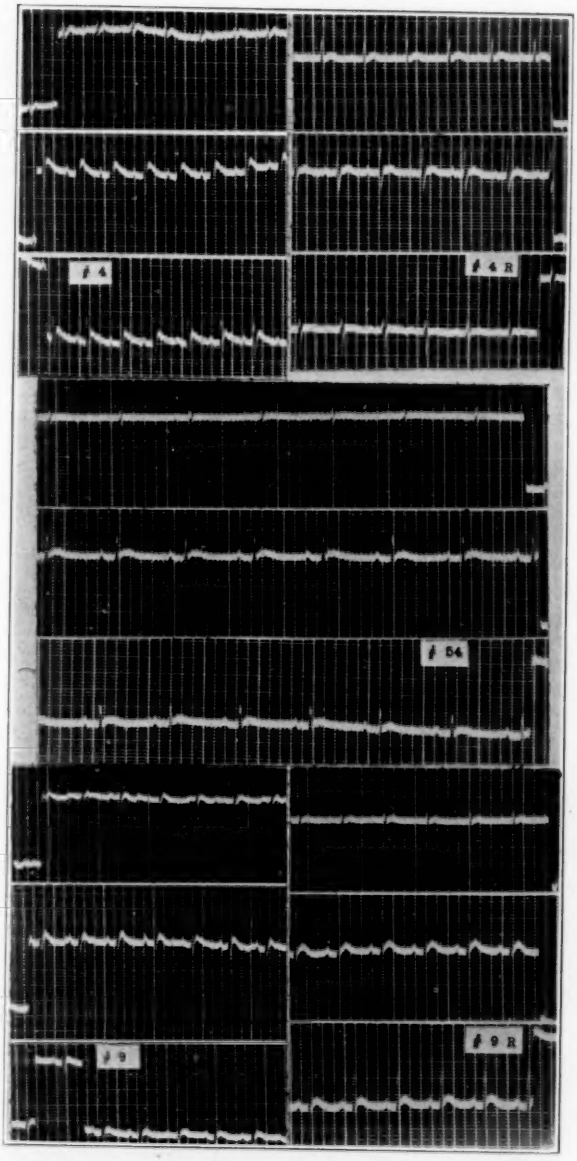

FIG. 3.—Electrocardiogram of animals before (Nos. 4, 9) and after (Nos. 4 R, 54, 9 R) thyroidectomy.

A general trend toward the slowing and lowering of all complexes can easily be seen. These graphs also serve to illustrate the inconsistency of changes of the electrical axis, as Rat 4 changed to the left, whereas Rat 9 changed to the right after thyroidectomy. The trend of the changes concerning heart rate and height of deflection is in full accord with myxedematous changes seen in human electrocardiograms.[2,4,6] As can be seen from graph No. 54 (Fig. 3), taken 6 months after thyroidectomy, there are extremely low-voltage QRS complexes with isoelectric T waves in Leads 2 and 3.

The slowing of the heart rate and the lowering of all complexes in cases of myxedema, are said, by some authors, to be due to a hydropericardium which however, could not be observed at autopsy of the 2 long-time thyroidectomized animals. The other, more likely, point of view is that these changes are produced by interstitial edema of the cardiac muscle, which would certainly tend to change its conductivity.[6]

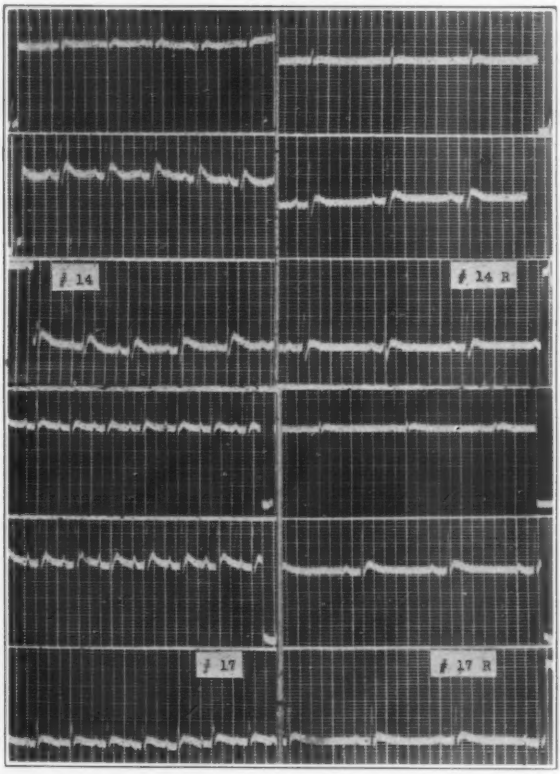

FIG. 4.—Electrocardiogram of animals before (Nos. 14, 17) and after (Nos. 14 R, 17 R) thiourea treatment.

The electrocardiographic changes following treatment with 1% thiourea for 3 weeks are illustrated by graphs No. 14 and 17, Figure 4.

Here, as in the case of the thyroidectomized animals, there is a decrease in heart rate; however, it is found to be much more pronounced after thiourea despite the fact that these animals had only been treated for 3 weeks. The conduction time shows a parallel increase and the T waves are found to be markedly lowered. These, like the majority of electrocardiograms after thiourea treatment show a decided change of the electrical axis to the right.

In complete contrast to the thyroidectomized animals, there is an increase in voltage of the R waves together with an increase of the total amplitude of the QRS complex (R+S).

It is well to remember however, that the decrease in amplitude of the ventricular complexes is an integral part of the "myxedema electrocardiogram.[2,4,6]"

In order to illustrate the partial parallelism and the marked partial discrepancy of electrocardiographic changes after thyroidectomy and after thiourea treatment, Table 6 was drawn up.

TABLE 6.—ELECTROCARDIOGRAPHIC CHANGES

	After thyroidectomy	After thiourea
Weight of rat	+31.2 ± 18	−20 ± 11.3
Heart rate	−11.8 ± 6.1	−98 ± 21.2
P–R interval	+0.003 ± 0.002	+0.012 ± 0.004
R_2	−0.137 ± 0.060	+0.034 ± 0.039
R + S	−2.9 ± 1.2	+1.6 ± 0.66
T_2	−0.054 ± 0.029	−0.092 ± 0.035

In this table the mean changes with their direction and deviation from the mean are recorded for each procedure.

Whereas thyroidectomized animals gained weight during the interval of 1 month, all thiourea treated animals lost weight. There was a drop in heart rate with increased conduction time after both procedures, which was however more marked after thiourea treatment. The R waves and the total amplitude of the ventricular complex (R+S) lost in voltage significantly after thyroidectomy, whereas the opposite could be observed after thiourea treatment. Finally, there was a characteristic drop in amplitude of the T waves after both procedures.

Although thyroidectomy produces electrocardiographic changes similar, if not identical, with those seen in human cases of myxedema, thiourea treatment duplicates this disease electrocardiographically only to a limited extent. This observation is in contrast to the views of Leblond and Hoff[7,8] who stated that 1% thiourea in drinking water given to rats produces cardiac changes equal in degree to those produced by thyroidectomy.

The difference in reaction to the two procedures could possibly be explained by a direct toxic action of thiourea on the body and on the heart in particular. This view would be partially supported by the fact that the animals lost weight during treatment. Another explanation would be that thyroxin is formed outside of the thyroid gland, a view previously expressed by Chapman[3] and Morton *et al.*[9]

Although the latter view would account for the comparatively greater severity and speed with which changes occur after thiourea

treatment, it would not account for the comparative increase in amplitude of the QRS complexes, which still remain unexplained.

Summary and Conclusions. 1. The average appearance of a rat electrocardiogram was established from the analysis of 50 graphs recorded by means of a string galvanometer with high vibration speed in conjunction with an electronic amplifier.

The mean heart rate was found to be 328 beats per minute, with a corresponding mean conduction time of 0.047 second.

The mean amplitude of the R waves in Lead 2 was found to be 0.463 millivolts, the mean voltage of T_2 0.106 millivolt.

The ranges of these measurements were found to be fairly wide and entirely unrelated to sex and age of the animals. The majority of graphs showed no axis deviation. There was a slight preponderance of a "tendency to the right" over "tendency to the left" in the lower weight groups, which however decreased on approaching the higher weight groups.

2. Electrocardiograms were studied on thyroidectomized animals and animals treated with 1% thiourea in drinking water.

The changes after thyroidectomy simulated in all respects changes seen in human cases of myxedema, *i. e.*, lowering of heart rate with increased conduction time and lessened amplitude of all positive waves. Animals, 3 weeks after thyroidectomy, showed these changes to a lesser extent than those thyroidectomized 6 months previously.

Treatment of normal rats with thiourea for a period of 3 weeks produced marked slowing of the heart rate with increased conduction time and lowered amplitudes of the T waves. However, there was a striking tendency to increase the voltage of the R waves in complete contrast to the expected myxedematous changes.

Although there was no consistent shift in axis deviation after thyroidectomy, there was a definite shift to the right in the majority of thiourea treated animals.

3. The more complete myxedema-like response obtained after thiourea treatment as compared to that elicited following thyroidectomy lends further substantiation to the extra-thyroidal production of thyroxin as proposed by Chapman[3] and Morton *et al.*[9]

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A STUDY OF THE RELATIONSHIP OF THE BASAL BODY TEMPERATURE TO THE BASAL METABOLIC RATE IN HOSPITALIZED PATIENTS

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The recent recommendation of the use of the basal body temperature in determining the time of ovulation[2,3,5,7,11,13,14,15,16] and the renewed clinical interest in the relationship of the body temperature

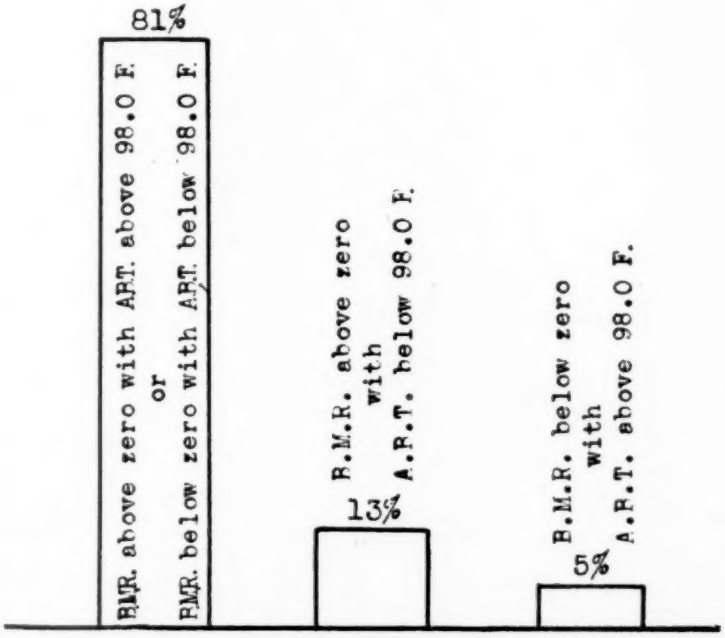
81%
B.M.R. above zero with A.B.T. above 98.0 F.
or
B.M.R. below zero with A.B.T. below 98.0 F.
13%
B.M.R. above zero with A.B.T. below 98.0 F.
5%
B.M.R. below zero with A.B.T. above 98.0 F.

Fig. 1.—Relationship between the basal metabolic rate (B.M.R.) and the average basal temperature (A.B.T.) in 255 Hospital Patients.

to the basal metabolic rate[1,6,8,12,14,16] occasioned this study. If, as has been suggested,[1] the basal body temperature is a better index for thyroid therapy than the basal metabolic rate, this is of particular importance now in industrial centers where patients cannot take time off from vital war work for determinations of the basal metabolic rate. The use of basal temperature graphs in timing the course of events in the human menstrual cycle apparently rests on adequate clinical and experimental evidence.[5,7,11,15] However, the evidence supporting an exact correlation between the average basal temperature and the basal metabolic rate requires additional consideration.

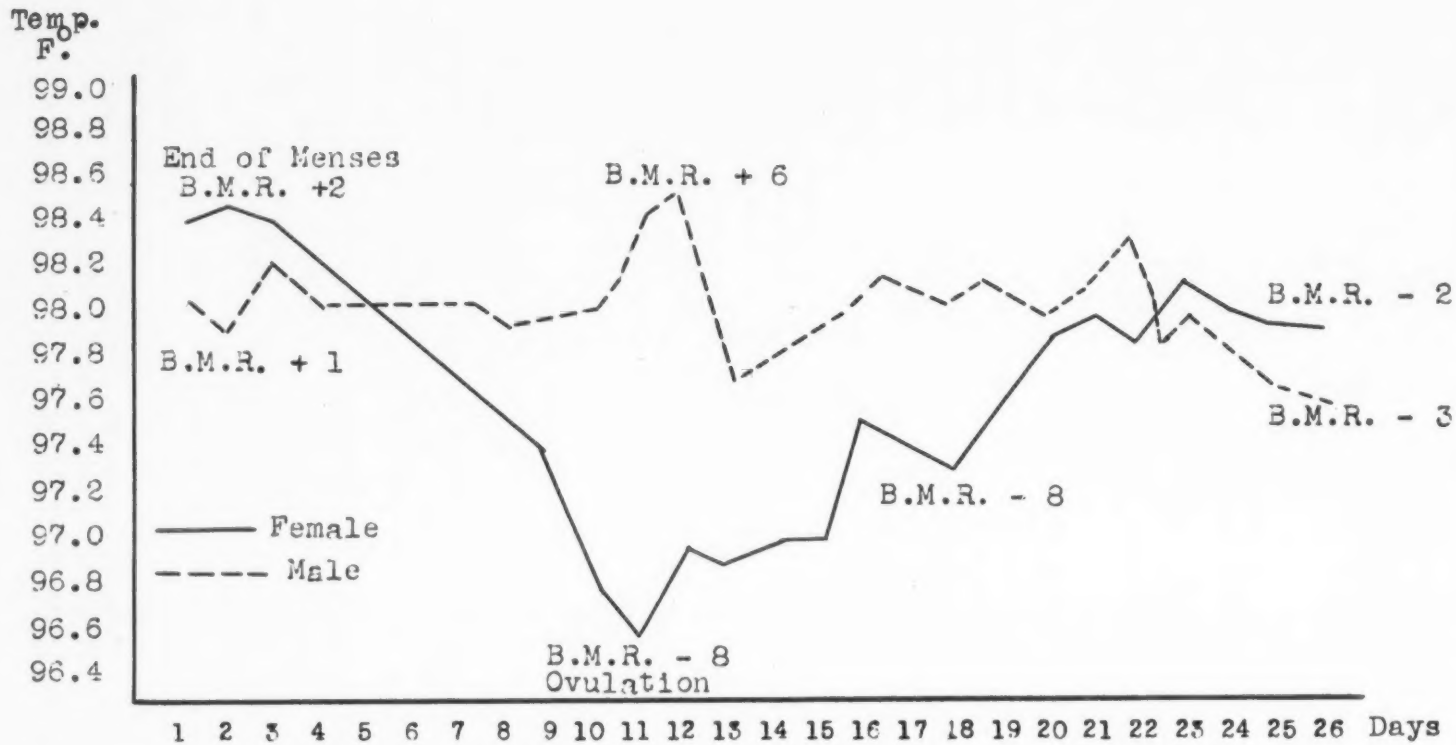

FIG. 2.—Daily variations in average basal temperatures and basal metabolic rate in male and female subject.

The work here reported was undertaken to determine what correlation, if any, exists in the afebrile hospital patient between the average basal temperature and the basal metabolic rate.

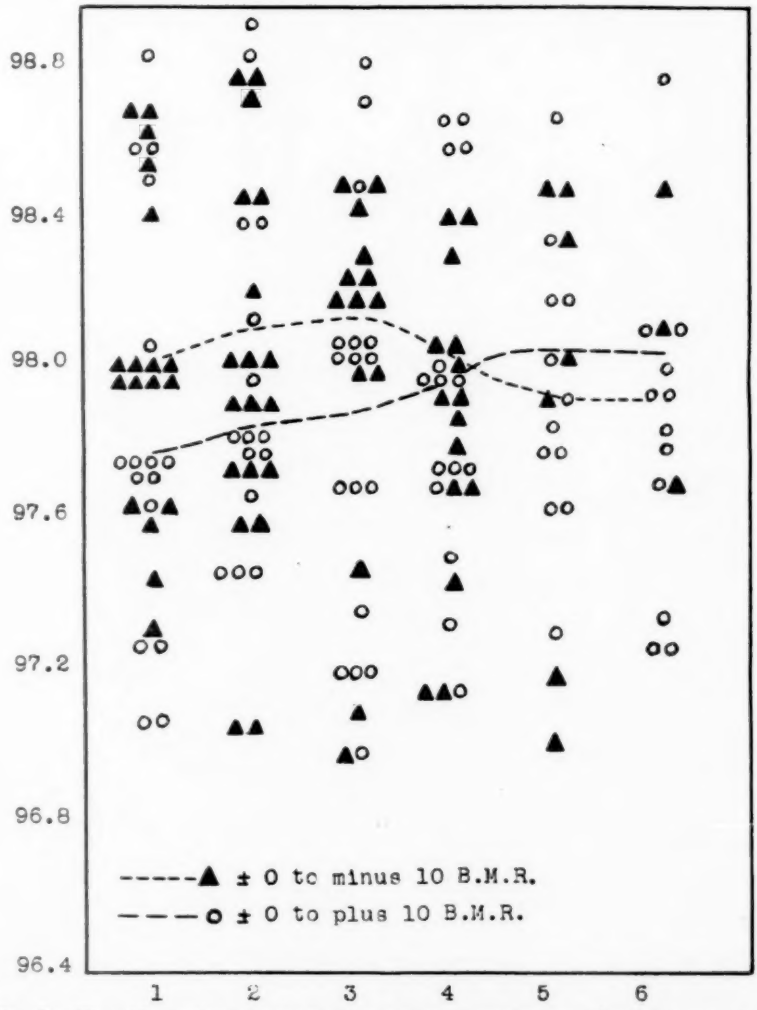

FIG. 3.—The wide variation in the basal temperature readings of individuals with +10 to −10 B.M.R. and the average basal temperature of these subjects.

Procedure. To determine this, the hospital records of individuals admitted for diagnostic investigation were reviewed.* Patients with febrile conditions were not included. The basal temperature determinations were taken as the early morning (7 to 8 A.M.) oral temperatures before the patient had been out of bed. The routinely determined metabolic rates were utilized. These were usually performed in duplicate or until consecutive determinations agreed satisfactorily.

In all, 255 patients were studied, 1150 basal temperature determina-

* Through the courtesy of Drs. A. H. Colwell, F. J. Gregg, and J. W. Shirer.

FIG. 2.—Daily variations in average basal temperatures and basal metabolic rate in male and

tions being made on the members of the group. Arbitrarily 98° F. was chosen as the normal basal temperature. Using this figure as normal, there was general agreement between the basal metabolic rate and the average basal temperature in 208 of the 255 patients

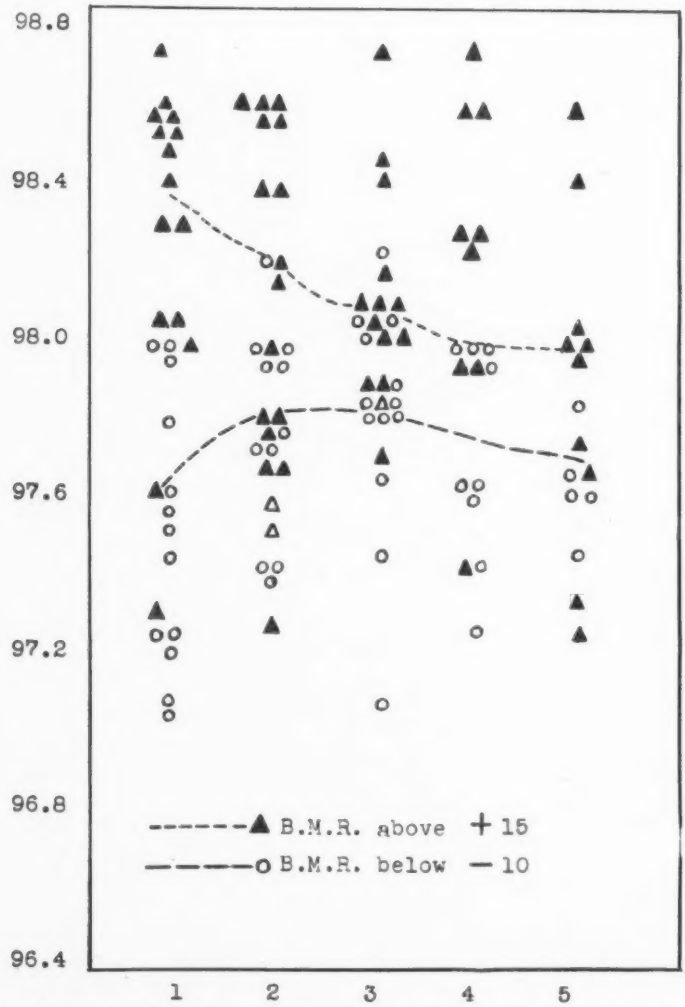

FIG. 4.—The wide variations in the basal temperature readings of individuals with high and low B.M.R. and the average basal temperature of these subjects.

(81%); *i. e.*, if the basal metabolic rate was zero or below, the average basal temperature was 98° F. or below (46%); or if the basal metabolic rate was zero or above, the average basal temperature was 98° F. or above (35%). In 34 patients (13%) the metabolic rate was above zero, although the average basal temperature was below 98° F. In 13 patients (5%) the basal temperature was above 98° F. with a negative basal metabolic rate. Figure 1 summarizes these findings.

The relatively high degree (81%) of agreement between the basal metabolic rate and the average basal temperature conforms to the well founded clinical observation that individuals with elevated metabolic rates generally have higher body temperatures (Fig. 4) and, indeed a low grade fever is frequently seen in thyrotoxicosis.[4] Similarly hypothyroidism in both man and animals is often accompanied by a relatively low average basal temperature.[4,8,12] However, it must be recognized that, while general agreement between the average basal temperature and the basal metabolic rate obtains, this generalization does not necessarily indicate that the average basal temperature can replace determinations of the basal metabolic rate.

Two reasons for this are apparent: (*a*) while in the normal male there is relatively little cyclic fluctuation in temperature, in the female the temperature variations due to hormonal activity are quite marked (Fig. 2) and, although these temperature variations are accompanied by a somewhat similar change in basal metabolic rate the two changes are not of strictly comparable magnitude;[14] (*b*) the second reason for the inability of the average basal temperature to be substituted for the basal metabolic rate is the tremendous overlapping that obtains both in the relatively normal group (± 10% B.M.R.) and those with definitely abnormal metabolic rates. Study of Figures 3 and 4 emphasizes the wide variations in basal temperature and indicates the difficulty encountered in attempting to give the average basal temperature the same significance as the basal metabolic rate. Although the temperature curve tends generally to be higher in the hyperthyroid individual and lower in the hypothyroid, this is not an invariable finding and there is a great deal of overlapping between the two groups. Study of Figure 4 indicates that while individuals with a high B.M.R. may have low basal temperatures, those with low B.M.R. seldom have basal temperatures above 98° F.

Summary and Conclusions. Evidence is presented to indicate that while the average basal temperature and the basal metabolic rate are in general agreement, individual determinations of the basal metabolic rate cannot be replaced by average basal temperatures in estimating the degree of metabolic activity.

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THE DANGER OF CONTINUED ARSENOTHERAPY IN CASES OF ERYTHEMA OF THE NINTH DAY

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The arsenical reaction termed by Milian[3] "erythema of the ninth day" is characterized principally by fever, malaise and a generalized eruption. Milian's concept that the reaction is due to "biotropism," that is an activation of latent "virus" by the drug, has few proponents today. The consensus is that sensitization to arsenic is the cause.

Moore[4] gives the following description: "The reaction occurs from 5—19 days after the first injection (average 7.8 days) and may follow any of the trivalent arsenicals. It is characterized by a polymorphic erythematous, scarlatiniform, or macular skin eruption accompanied by fever (101°—105° F.), sore throat, headache, malaise, diarrhea, stiffness of the neck and evidence of lymphoid hyperplasia. Its average duration is six days."

There appears to be an inadequate understanding, among practitioners, of the significance of this reaction, particularly of the scope of the disturbance created. Fourteen cases are being reported in which the prompt resumption of arsenical treatment was followed by severe parenchymatous injury. Issue may be taken with the inclusion of some of these cases in the category of "erythema of the 9th day," since no eruption was observed.

Table 1 presents pertinent details. All patients were male soldiers, and none had ever received more arsenic than is stated in the table. They were treated by the then routine antisyphilitic schedule of the Army. For present purposes, only the first 5 weeks of this schedule

Table 1.—Analysis of Data in 14 Cases

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age	20	24	32	20	37	20	18	18	25	30	23	19	20	22
Stage of disease	SPP	EL	LL	SNP	SNP	EL	EL	SNP	EL	LL	SNP	EL	EL	EL
Doses of mapharsen before appearance of "Milian" reaction	3	3	3	5	4	4	3	5	4	5	3	4	3	4
Days between first mapharsen injection and appearance of "Milian" reaction	7	8	9	9	10	10	7	9	7	11	6	9	9	10
Eruption	0	0	+	0	+	0	0	+	0	0	0	0	0	0
Additional doses of mapharsen after the "Milian" reaction	2	1	2	2	1	1	1	1	1	2	2	1	1	3
Days between first mapharsen injection and detection of parenchymatous injury	14	14	17	24	13	20	11	16	14	21	17	12	14	24
Type of parenchymatous injury	J N	J N	J N	A	J	A J N	J N	A N	J	J	J	J	J N	J N

SNP, seronegative primary syphilis; SPP, seropositive primary syphilis; EL, early latent syphilis; LL, late laten syphilis; J, jaundice; A, agranulocytosis; N, nephritis.

need to be detailed. Mapharsen was given twice weekly and bismuth subsalicylate once weekly. The maximal dose of mapharsen, 0.06 gm., was generally employed, although frequently the initial dose was 0.03 gm. or 0.04 gm.

The reaction occurred 6 to 11 days (average 8.6 days) after the first dose of mapharsen. In 6 cases, it appeared after 3 doses of the drug

had been administered, in 5 cases after 4 doses, and in 3 cases after 5 doses.

Table 2 is a compilation of the symptoms and signs observed in the 14 patients. The only symptoms common to all were fever, headache and weakness. Chills or chilly sensations and gastro-intestinal symptoms were frequent. Five patients had well-marked injection of the conjunctivas with photophobia, and 3 had puffiness of the eyelids and the upper part of the face. Two patients were irrational and had rigidity of the neck, so that a diagnosis of meningitis was considered.

TABLE 2.—SYMPTOMS AND SIGNS OBSERVED IN 14 PATIENTS WITH ERYTHEMA OF THE 9TH DAY

Symptom or sign	No. of patients affected
Fever	14
Headache	14
Weakness	14
Nausea	11
Chills or chilly sensations	7
Vomiting	7
Injection of conjunctivas with photophobia	5
Abdominal pain	3
Edema about eyes and upper part of face	3
Injection of pharynx	3
Cutaneous eruption	3
Substernal oppression	2
Irrational	2
Stiffness of neck	2
Enlarged, tender cervical nodes	2
Anorexia	2
Sore throat	2
Backache	1
Neuritis	1

Most interesting was the infrequency of a cutaneous eruption. Both white patients had a generalized morbilliform eruption and 1 of the Negro patients, a mulatto, had a faint pink macular eruption. It is my belief that the reaction was of the same nature in all. In the Negro, the deep natural pigmentation may obscure the pallid, rose-colored macular or scarlatiniform eruption, and also the eruption may be so transient that it will have disappeared by the time the patient is examined. It is entirely possible that the eruption is not an essential part of the syndrome.

In every instance, mapharsen was administered shortly after recovery from the initial reaction, sometimes after a rest interval of a week. Usually there was a prompt recurrence of the original symptoms, but the eruption did not reappear. In only 2 cases was the subsequent dose of mapharsen reduced, to 0.03 and 0.04 gm. respectively, while in the remaining 12 cases the full dose of 0.06 gm. was administered. It was after this additional arsenic that the evidences of parenchymatous damage became apparent (Table 1). The serious complications were observed from 11 to 24 days following the first dose of arsenic, when additional drug had been given a relatively short interval (from 3 to 8 days) after the initial febrile episode. They included

hepatitis, agranulocytosis and nephritis, alone or in combination (Table 1).

All patients recovered, some only after a prolonged and severe illness. For 2 patients, it was subsequently recommended that bismuth alone be given for 4 months, and thereafter arsenoxide with extreme caution. The course of these patients is unknown. The remaining 12 patients received intensive treatment with penicillin (either 1.2 or 2.4 million units of penicillin in 7½ days) without reaction. Their therapeutic result cannot be evaluated at this time.

It is noteworthy that 7 of the 14 patients were either in the hospital at the time of the initial reaction or were admitted because of it, and that the reaction was misinterpreted or minimized. In 1 case the diagnosis was German measles, in another it was common cold, and in the remaining 5 it was thought to be a relatively minor reaction to arsenic. One case is reported in some detail:

Case 8. A white male, aged 18 years, was admitted to the hospital with seronegative primary syphilis. He received the following treatment: August 8, 1944, mapharsen 0.04 gm.; August 10, mapharsen 0.06 gm.; August 12, mapharsen 0.06 gm.; August 14, mapharsen 0.06 gm. He was then discharged, since his penile lesion was healed. During this period there had been no intolerance to the arsenical.

On August 17 (9 days after the first injection), he was given mapharsen 0.06 gm., and about 1 hour later he became weak and dizzy, and complained of feverishness, severe frontal headache, generalized aching pains, nausea and vomiting, and substernal oppression. He was readmitted to the hospital.

Examination revealed injection of the conjunctivas and pharynx, palpable and tender submaxillary nodes, a generalized rose-colored macular eruption and temperature of 103.4° F. The spinal fluid was normal. The white blood cells, examined on two occasions, were 7250 and 7650, with 61 and 53% neutrophils respectively. The urine contained 2+ albumin. A diagnosis of German measles (this disease was then endemic) was made. The fever and eruption had disappeared by August 22, and on August 24 the patient was discharged.

On August 24 he was given mapharsen 0.06 gm., and within an hour he developed severe frontal headache, nausea, vomiting and malaise. He was again admitted to the hospital and found to have fever, puffing of the face, injection of the conjunctivas and pharynx, soft tender nodes under both angles of the jaw, and a blood pressure of 90/50. The urine repeatedly contained albumin, casts and red blood cells. The first white blood cell count was 4100 with 44% neutrophils, but within 3 days the count was 4100 with 3% neutrophils, 1% each of eosinophils and basophils, 86% lymphocytes, and 9% monocytes. Subsequently he developed total agranulocytosis, and there appeared gangrenous pyogenic lesions of the forehead and neck. He was treated with pentnucleotide and repeated blood tranfusions with little improvement. It was decided to use penicillin in an effort to control the pyodermas, and he was given a total of 2,880,000 units from August 30 to September 8, 1944. He made a prompt and complete recovery, the pyodermas healing rapidly, and the blood returning to normal. It is anticipated that the penicillin will be "curative" of the syphilitic infection.

Comment. Fever in the first 2 or 3 weeks of arsenotherapy may be of different origins. After the initial dose of arsenic, it is usually a manifestation of the systemic Herxheimer reaction. This is especially true of primary and secondary syphilis, less so of latent and late syphilis. The Herxheimer reaction (seen also with penicillin) is ascribed

to massive destruction of treponemes in the circulating blood with release of their toxins or proteins. It does not recur after subsequent injections.

Fever after the second or third, or later, injections of arsenic must be regarded as evidence of toxic reaction or intercurrent infection. It is the intent of this paper to indicate that the safest course is to consider any febrile episode (except the Herxheimer reaction), especially in the first 3 weeks of arsenotherapy, a probable manifestation of sensitivity to arsenic. This is particularly true when the entire syndrome of "erythema of the 9th day" is present. However, it appears to apply with equal force to those cases in which no rash is detected. It is in the clinic and the private physician's office, where patients receive ambulatory treatment and cannot be under close surveillance, that greater awareness of this syndrome is needed. Strict attention should be paid to all reactions following the second and subsequent injections of arsenic, and these should not be minimized.

Erythema of the 9th day is transitory, but nevertheless profound in its disturbances, and not to be underestimated. It is generally held that bismuth may be continued but that arsenic must be deferred for a period of 4 to 12 weeks, and then used cautiously. Many patients will then be found tolerant of the drug. Thus, Cañizares and Thomas[1] state that in their series later reactions were chiefly nitritoid or gastrointestinal. They quote Stokes as having reported a case of exfoliative dermatitis developing when arsenicals were continued. In a later paper, Thomas and Cañizares[6] report 2 cases in which the eruption and general symptoms recurred when arsenic was again given.

Cole, Heisel and Stroud[2] describe a "fever-conjunctival injection-facial edema syndrome" which appeared in 24 patients receiving mapharsen three times weekly. In 17 there were fever, chills, photophobia, nausea, vomiting and general malaise. Shortly after the onset of symptoms the patients showed some conjunctival injection and edema of the face. These symptoms came on after the fifth or sixth injection, and from 9 to 12 days after the first injection. One patient developed icterus which lasted 15 days. In another case an attempt to give neoarsphenamine 12 days after the initial reaction reproduced the reaction along with profound muscular weakness. Three months after the original reaction this patient tolerated 0.01 gm. of mapharsen well. No mention is made of any eruption, and the race of the patients is not stated. This reaction parallels in most respects those described in this paper.

Peters[5] reviewed 54 cases of "erythema of the 9th day," in 2 of which (both Negroes) no eruption was present. Eighteen other colored patients and 34 white patients had a rash. Peters describes the occurrence of visceral reactions along with the initial reaction, before the administration of additional arsenic. These were jaundice in 7 patients, hepatomegaly without jaundice in 4, nephritis in 2, splenomegaly in 1, and granulocytopenia in 1. Of the 36 patients who received further arsenotherapy, 70% had reactions; "53% had serious delayed complications which consisted of dermatitis with and

without exfoliation, jaundice, intolerance to several trivalent arsenical drugs, fever, nitritoid reactions, and recurrent erythema of the 9th day."

It is possible that some of the 14 cases reported here might have shown visceral damage, without additional arsenic. Nevertheless, this arsenic was an added insult, aggravating the already present, but subclinical, parenchymatous injury.

Whether we call this reaction the Milian reaction, "erythema of the 9th day," "early arsenical erythema," or the "fever-conjunctivitis-facial edema syndrome," is of little importance. What is most pressing is that it be recognized as a portentous reaction and regarded with the utmost seriousness. This is particularly vital in view of the ease with which the reaction is minimized or misinterpreted. Serious visceral injury might have been prevented, and certainly would not have been aggravated, if the cases reported had been correctly diagnosed and properly managed.

While it is true that penicillin is rapidly replacing the arsenicals as the therapeutic agent of choice in syphilis, a considerable amount of arsenic will probably be used for some time. The Milian reaction has been observed in diseases other than syphilis, and the arsenicals may continue to be used in non-syphilitic diseases and in certain phases of syphilis.

Summary. 1. Fourteen cases of characteristic reaction occurring early in the course of arsenotherapy (6 to 11 days after the first injection) are reported.

2. Only 3 of the 14 patients had a concomitant eruption.

3. The relationship of this reaction to "erythema of the 9th day" is discussed.

4. In all 14 patients early continuation of arsenic after the initial reaction led to serious parenchymatous damage, in the form of jaundice, agranulocytosis, with or without nephritis.

5. The ease with which the reaction is misinterpreted or minimized is indicated, and the need for careful evaluation of fever in the early phases of arsenotherapy is stressed.

6. Twelve of the 14 patients subsequently received an intensive course of penicillin without untoward reaction.

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POSSIBLE EFFECTIVENESS OF THE L. CASEI FACTOR ("FOLIC ACID") CONCENTRATES ON REFRACTORY ANEMIA AND LEUKOPENIA, WITH PARTICULAR REFERENCE TO LEUKOPENIA FOLLOWING RADIATION THERAPY

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The effectiveness of the *L. casei* factor and its concentrates in the treatment of leukopenia in rats receiving a deficient diet plus sulfonamides has been fully established.[1,2,3] These results suggested a clinical trial of *L. casei* factor concentrates in patients exhibiting leukopenia of various cause. In some of these rat studies by Sebrell and his coworkers, not only leukopenia but also an anemia was noted. It was, therefore, determined to employ the material in patients suffering from refractory or aplastic anemia as well as in those in which leukopenia alone of various cause was exhibited. Since 20 micrograms of *L. casei* factor daily for 4 days was quite adequate to correct either leukopenia or anemia, or both, to normal in the rat,[3] an arbitrary dosage of 5 mg. per day for a period of 6 days was decided upon for the human studies. The concentrates available to us contained, respectively, 5 mg. in 7 cc., and 5 mg. in 10 cc.* It was found that this amount was taken without difficulty and well tolerated given in ½ glass of milk or tomato juice. In most instances tomato juice was employed. Half of the material was given in the forenoon and half in the late afternoon, in each instance. A total of 17 cases have been studied in this way. The distribution of these cases in terms of clinical diagnosis was as follows:

1. N. W., ♂, 31 (U.H. 739751). Refractory anemia; insecticide exposure.
2. H. G., ♂, 68 (U.H. 740034). Refractory anemia; insecticide exposure.
3. C. E., ♂, 70 (U.H. 740368). Refractory anemia; insecticide exposure.

* These concentrates of the particular *L. casei* factor described by Hutchings, Stokstad, Bohonos and Slobodkin[5] were supplied through the courtesy of E. L. R. Stokstad of Lederle Laboratories, Inc. In addition to microbiologic potency, the biologic activity of these concentrates was determined. Rats which became leukopenic and granulocytopenic on a purified diet containing succinyl sulfathiazole, were treated with 20 μg. per day of *L. casei* factor for 4 days. This was sufficient to bring the leukocyte count of such rats from below 4000, with not more than 5 per cent granulocytes, to 10,000 or higher, with more than 20% granulocytes.

4. H. K., ♀, 28 (U.H. 601008). Refractory anemia; dilantin therapy with skin rash and fever 3 years prior to symptoms of anemia.
5. E. P., ♂, 64 (U.H. 743406). Neutropenia; no known causative factors.
6. B. D., ♀, 19 (U.H. 736826). Refractory anemia; no known causative factors.
7. C. A., ♂, 61 (U.H. 739736). Refractory anemia; insecticide exposure.
8. P. J., ♂, 7 (U.H. 744188). Refractory anemia; following pneumonia and sulfonamide therapy.
9. B. W., ♂, 39 (U.H. 746428). Hodgkin's disease; Roentgen ray leukopenia.
10. B. F., ♀, 23 (U.H. 739188). Rheumatic fever; leukopenia following sulfonamide therapy.
11. W. K., ♂, 67. Polycythemia vera; leukopenia following total body radiation.
12. C. H., ♀, 60 (U.H. 747344). Carcinoma of cervix uteri; Roentgen ray leukopenia.
13. D. K., ♀, 43 (U.H. 740434). Carcinoma of cervix uteri; Roentgen ray leukopenia.
14. M. M., ♀, 67 (U.H. 741624). Carcinoma of cervix uteri; Roentgen ray leukopenia.
15. I. D. W., ♀, 29 (U.H. 743377). Carcinoma of cervix uteri; Roentgen ray leukopenia.
16. I. W., ♀, 41 (U.H. 743337). Carcinoma of cervix uteri; Roentgen ray leukopenia.
17. E. B., ♀, 62 (U.H. 739903). Carcinoma of cervix uteri; Roentgen ray leukopenia.

Additional data for the first 10 cases of the above group (1 to 10 inclusive), and for Cases 12 to 17, are given in Table 1 and Figure 1, respectively. The clinical and laboratory data for Case 11* are given in the following:

Case 11. W. K., ♂, 67. Polycythemia vera with hyperleukocytosis. Condition first recognized in 1938 at which time the hemoglobin was 137% (Dare) and the red blood cells were 8.49 millions per c.mm. The leukocytes at that time were 15,050 with 87% neutrophils. The spleen and liver were moderately enlarged. Roentgen ray examination of the gastro-intestinal tract revealed a duodenal ulcer with crater. Roentgen ray therapy totaling 900 r was administered over two gastric portals (in 1938). Blood-letting was performed frequently. During the last 2 years the hemoglobin had decreased so that a hypochromic microcytic type of polycythemia resulted. The leukocytes had steadily risen during this period to a range of 80,000 to 100,000, with 85 to 88% neutrophils, but no evidence of leukemia in the peripheral blood or sternal bone marrow had appeared. Further data in this case are given in Table 2.

Results. The results in the first 10 cases, comprising the refractory anemia and toxic leukopenia group, were entirely negative (Table 1).

* The data from this case were made available to us through the courtesy of Dr. Leon Jacobson, Department of Medicine, University of Chicago.

The only changes observed which might be construed as related to the administration of folic acid were in the group of leukopenias following Roentgen ray therapy (Cases 11 to 17, inclusive). The data are shown in Table 2 and Figure 1.

Discussion. Insofar as the refractory anemias were concerned, it was scarcely hoped that the *L. casei* factor concentrates would achieve the beneficial effects observed experimentally,[1,2,3] since there was no reason to believe that a dietary factor was operative in the human disease. Nevertheless, the unknown pathogenesis of human refractory anemia,[4] and, as the name implies, the lack of a successful therapeutic agent made the present trial of *L. casei* factor concentrates a mandatory experiment. It is not possible, on the basis of the condition of the bone marrow, to differentiate between human aplastic anemia and the anemia and leukopenia found in rats receiving sulfonamides. Rat marrows may at times present a picture of actual hyperplasia with a preponderance of immature forms;[6] but at other times[1] the picture is one of profound hypoplasia, very similar to the picture in human aplastic anemia. With respect to a possible dietary factor we were particularly interested in Case 8 of the present series, the only one in which there was a definite history of dietary deficiency. There were, however, no collateral evidences of deficiency. Since this case was that of a child in which infection, sulfonamide therapy and poor diet all had to be considered as possible etiologic factors, we were somewhat more hopeful of a beneficial effect following the folic acid concentrate, but as seen in Table 1, no effect was observed.

At the outset it was decided to include the cases of Roentgen ray leukopenia mainly from the standpoint of permitting comparison with a group in which the etiology was better understood, but with even less hope of benefit than in the more heterogeneous group of cases (1 to 10 inclusive). It was surprising, therefore, to observe a rather consistent increase of the leukocytes following the administration of folic acid concentrate in Cases 11 to 17; *i. e.*, those in which leukopenia resulted from Roentgen ray therapy.

The question at once arises as to whether these increases might not have occurred without the folic acid. In certain instances the application of radium increased the difficulty of interpretation. This is especially true in Cases 12 and 13. In Case 12 a definite rise was observed following folic acid, and then, with continued Roentgen ray, the count returned to just below 2000. Folic acid concentrate was resumed but radium was applied just before the second increase of the leukocytes occurred. In Case 13 the radium was implanted in the middle of the period of folic acid administration and prior to any increase in leukocytes. Shortly thereafter a striking increase occurred and since similar increases are at times noted when radium alone has been used, one cannot, of course, ascribe the rise to the folic acid. In Cases 14 and 16, similar marked increases were observed but in each of these an increase had already taken place before the radium was implanted. One of the most impressive features of the study was the elevation of leukocytes following folic acid in spite of continued radia-

TABLE 1—BLOOD CHANGES AFTER FOLIC ACID ADMINISTRATION

Case No.	Age	Sex	Diagnosis	Blood findings before folic acid		Blood findings (days after commencement of folic acid)						
						1	3	6	8	12	19	27
1 (N. W.)	31	♂	Refrac. anemia poss. due to insecticide; duration 6 mos.	Hb. in gm. per 100 cc.	4.1	4.0	3.8	4.1	5.8	8.7	14.5	10.2
				WBC per c.mm.	1900	1500	1500	1050	1250	2100	2300	1200
				Neutrophils, %	31	34	34	28	31	12		8
				Lymphocytes, %	69	66	66	72	68	87	87	88
				Blood transfusions in cc.				500	500	500	Dis. unimpr.	
						1	3	5	7	8	9	12
2 (H. G.)	68	♂	Refrac. anemia poss. due to insecticide; duration 5 mos.	Hb. in gm. per 100 cc.	3.3	3.18	2.78	2.58	2.9	2.74	3.2	3.9
				WBC per c.mm.	2400	2300	1650	2000	2400	2250	2750	1700
				Neutrophils, %	37	36	54	48	49	56	58	62
				Lymphocytes, %	63	64	44	52	50	44	40	38
				Blood transfusions in cc.						500	500	500
											Dis. unimpr.	
						1	3	5	6	8	10	11
3 (C. E.)	70	♂	Refrac. anemia poss. due to insecticide; duration at least 9 mos.	Hb. in gm. per 100 cc.	11.3	9.7	9.7	10.1	9.4	9.2	9.1	9.1
				WBC per c.mm.	1200	800	1300	1100	750	1000	1500	950
				Neutrophils, %	23	25	24	54	54	40	28	30
				Lymphocytes, %	77	72	74	44	39	56	70	70
											Died	
						1	3	5	7	9	10	21
4 (H. K.)	28	♀	Refrac. anemia of unknown etiology (lengthy mebaral-dilantin therapy for epilepsy); duration 1 yr.	Hb. in gm. per 100 cc.	6.7	6.0	5.7	5.0	4.4	5.0	6.0	5.9
				WBC per c.mm.	1400	1200	3100	2450	2400	1200	2500	1500
				Neutrophils, %	14	10	14	19	27	24	20	6
				Lymphocytes, %	86	90	85	75	71	76	77	94
				Blood transfusions in cc.						500	500	
							Continuous fever 101–103° F. Frequent nosebleeds. Died.					
						1	3	5	7	10	11	
5 (E. P.)	64	♂	Neutropenia of unknown etiology, poss. atypical leukemia; necropsy inconclusive	Hb. in gm. per 100 cc.	12.0					7.3	7.7	
				WBC per c.mm.	1100	1350	2000	1950	1450	700	1250	
				Neutrophils, %	34	32	29	26	16	28	26	
				Lymphocytes, %	66	68	71	70	84	72	74	
				Reticulocytes, %	0		0.2		0.2		0.2	Died
						1	2	4	7	9	10	70
6	19	♀	Refrac., idiopathic	Hb. in gm. per 100 cc.	6.7	6.5	6.5	7.0	7.0	7.2	7.5	6.0

(E. P.)			known etiology, poss. atypical leukemia; necropsy inconclusive	WBC per c.mm.	1100	1350	2000	1950	1450	700	1250	
				Neutrophils, %	34	32	29	26	16	28	26	
				Lymphocytes, %	66	68	71	70	84	72	74	
				Reticulocytes, %	0		0.2		0.2		0.2	Died
						1	**2**	**4**	**7**	**9**	**10**	**70**
6 (B. D.)	19	♀	Refrac., idiopathic anemia of 2 yrs. duration	Hb. in gm. per 100 cc.	6.7	6.5	6.5	7.0	7.0	7.2	7.5	6.0
				WBC per c.mm.	3650	3200	2200	2250	2550	2950	3650	3700
				Neutrophils, %	50	56	51	58	36	32	30	58
				Lymphocytes, %	48	44	48	42	64	66	69	42
				Reticulocytes, %	3.2		2.8	3.8	4.0		3.2	
				Platelets per c.mm.	144,000				134,000		120,000	
						1	**2**	**4**	**7**	**12**	**15**	**22**
7 (C. A.)	61	♂	Refrac. anemia of unknown cause; 1½ yrs. duration	Hb. in gm. per 100 cc.	8.9	8.4	8.9	7.7	8.6	7.5	8.3	8.9
				WBC per c.mm.	4200	3900	4000	4000	3650	3500		
				Neutrophils, %	62	56	56	52	33			
				Lymphocytes, %	35	44	42	46	64			
				Reticulocytes, %	0.8	0.7	1.2	1.8	1.5	1.0	0.8	0.7
				Platelets per c.mm.	150,000	133,000			144,000		Unimpr.	
						1	**2**	**4**	**6**	**7**	**8**	**26**
8 (P. J.)	7	♂	Refrac. anemia of unknown cause; 1 yr. duration; purpura marked (platelets 24,000 per c.mm.)	Hb. in gm. per 100 cc.	7.2	6.6	6.5	5.6	5.6	4.4	7.1	7.8
				WBC per c.mm.	2500	1900	2400	2450	2550	1850	2000	1650
				Neutrophils, %	28	20	26	42	50	38	37	30
				Lymphocytes, %	72	79	73	58	50	62	63	62
				Reticulocytes, %	0.9	1.2		1.1	1.6		1.4	
				Blood transfusions in cc.						500	Unimpr.	
						1	**3**	**6**	**7**	**8**	**11**	**32**
9 (B. W.)	39	♂	Hodgkin's disease; severe leukopenia following extensive Roentgen ray treatment; marked fever	WBC per c.mm.	750	650	1000	950	850	750	950	750
				Neutrophils, %	67	69	68	65	63	62	59	
				Lymphocytes, %	29	29	29	32	35	34	38	
						2	**4**	**7**	**9**	**11**	**31**	**68**
10 (B. F.)	23	♀	Rheum. fever; leukopenia for 2½ yrs. following 14 gm. sulfathiazole in 3 days; also persistent rheum. activity varying in degree	Hb. in gm. per 100 cc.	11.3	11.2	11.7	11.0	10.8	11.0	11.3	12.3
				WBC per c.mm.	2000	1600	2100	2400	2300	2850	2550	2700
				Neutrophils, %	8	10	14	15	15	21	16	45
				Lymphocytes, %	90	90	85	80	82	79	84	53

TABLE 2.—LEUKOPENIA IN A CASE OF POLYCYTHEMIA VERA FOLLOWING TOTAL BODY RADIATION (CASE 11)

Date	Hb. (gm. per 100 cc.)	RBC (mill. per c.mm.)	WBC (per c.mm.)	Neutrophils (%)	Lymph. (%)	Mono. (%)	Eos. (%)	Band forms (%)	Retic. (%)	Platelets (per c.mm.)	Remarks
5–12	..	..	76,800	87	4	3	6	..	..	..	
5–17	11.8	5.80	65,650	84	7	4	5	..	..	..	Total body radiation—
5–19	12.1	6.20	102,000	84	6	..	6	4	2.1	1,975,000	(200 kv.) 250 r total,
5–23	11.6	5.50	77,800	84	4	1	8	3	1.0	1,929,600	in divided doses
5–27	11.0	5.10	44,000	77	4	..	5	13	1.2		
6–2	11.2	5.16	19,500	83	8	..	4	5	0.7	690,000	
6–7	11.6	5.44	18,300	72	4	..	1	23	0.5	392,700	
6–13	10.0	5.68	5,600	64	13	..	3	20	0.2	53,900	
6–16	10.5	5.35	3,900	61	19	..	5	15	0.3	77,000	
6–23	10.9	5.76	1,400	18	43	2	31	6	0.2	146,300	
6–27	10.0	4.57	650	9	57	8	22	4	0.1	170,500	
6–29	..	..	1,400	8	42	10	8	22	..	121,000	
6–30	11.5	5.14	1,550	13	44	4	5	34	0.2	..	
7–1	..	..	1,850	19	40	12	4	25	..	..	Folic acid
7–2	..	..	2,600	28	38	7	3	24	..	..	
7–3	10.5	4.95	2,650	28	23	27	1	28	0.3	..	
7–4	..	..	3,100	37	30	23	..	10	..	..	
7–5	9.8	4.66	3,700	36	33	16	2	11	0.5		
7–7	10.0	4.85	7,050	62	..	11	12	15	0.4	246,400	
7–11	10.9	4.22	6,400	72	13	15	..	..	0.5	286,000	
7–18	11.0	4.24	7,500	76	16	5	..	3	1.0	247,000	

tion, as particularly well exemplified in Cases 12, 16 and 17. It has not been possible to obtain control data on this point since, in the past, radiation has not been continued or resumed in the presence of such relatively severe leukopenia as was noted in these cases. It is the gynecologist's (J. L. McK.) impression, on the basis of past experience, that to have continued Roentgen ray therapy under ordinary circumstances in these cases, would have been inadvisable. In Case 13 it

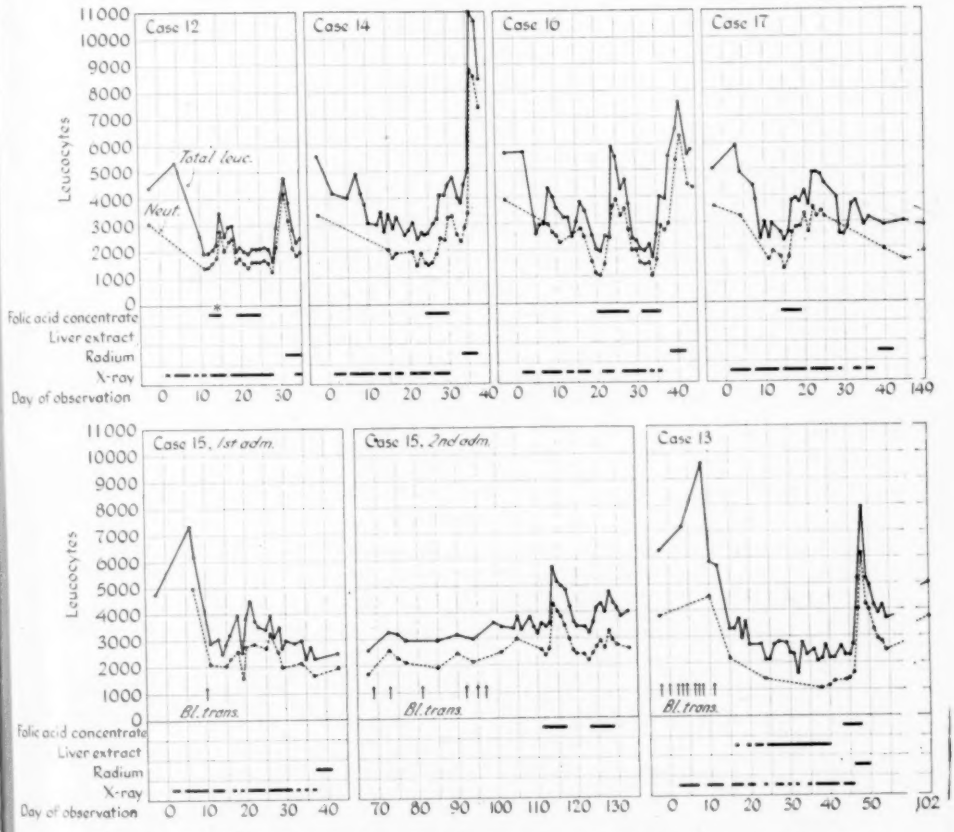

FIG. 1.—Total leukocyte and neutrophil counts in 6 cases of leukopenia following intensive Roentgen ray therapy for carcinoma of the cervix uteri. In each instance a total of 3000 tissue Roentgens was given during the periods indicated. The term folic acid concentrate refers in all instances to the *L. casei* factor (see p. 1).

will be noted that liver extract was given for a considerable period, along with intermittent Roentgen ray therapy, and that during this period the leukopenia was fairly well stabilized. The liver extract used undoubtedly provided small amounts of folic acid although no information is available as to the exact amount. It may be noted that in previous cases, some encouragement was gained when crude liver extracts of this type were used, although only in the sense that the leukocyte count stabilized itself or rose slowly.

One of the most suggestive results in the present group of cases is that seen in Figure 1 (Case 15) in which a mild leukopenia persisted for over 3 months after Roentgen ray therapy for carcinoma of the cervix. The administration of folic acid concentrate in this case was followed on 2 occasions by definite elevations of the leukocyte count. No other stimulating factors were recognized.

We do not wish to draw any conclusions from the results which have just been discussed. It is fully realized that the increase in leukocytes noted in the Roentgen ray leukopenia group has not been proven to be due to the administration of folic acid. At the same time, it is believed that the present results justify further investigation as soon as folic acid becomes available in adequate amounts.

Summary. *L. casei* factor ("folic acid") concentrate has been administered orally in 17 cases of refractory anemia or leukopenia. No effect was observed in the 8 cases of refractory anemia, nor in 1 case of leukopenia persisting after sulfonamide therapy. Elevations of the leukocyte count were noted in each of 6 cases with leukopenia resulting from local intensive Roentgen ray therapy for carcinoma of the cervix, and in 1 case of polycythemia vera receiving total body radiation. No effect was observed in 1 case of Hodgkin's disease exhibiting severe leukopenia following intensive Roentgen ray therapy to various parts of the body.

No conclusions may be drawn from the present results. They are communicated at this time for the purpose of stimulating further study of the possible effectiveness of folic acid in the treatment of certain forms of leukopenia, especially that resulting from radiation.

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SYNCHRONIZATION OF NEUROTIC BEHAVIOR PATTERNS

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I. *The neurotic harbors an unconscious "repetition machine."* Every neurotic can be compared to a person carrying around constantly *one* phonograph record and constantly on the lookout for a phonograph

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on which to play his only tune. In this simile the one and only record represents the basic *unconscious* neurotic tendency; the phonograph stands for the other person with whom the neurotic pattern can be repeated. Expressed differently, Freudian psychoanalysis has proven in 50 years of clinical experience that certain unconscious behavior patterns acquired in early childhood become petrified, and under the pressure of the "unconscious repetition compulsion" (Freud) are repeated throughout the remainder of life with eternal monotony—and completely without conscious awareness of that repetition. Thus, the unconscious "repetition machine" reels off the unconscious behavior pattern.

All of this has been known to analysts for many years. The problems which shall be discussed in this paper are:

1. The interrelation of 2 persons repeating respectively corresponding neurotic behavior patterns.
2. The specificity of choice of object for this repetitiveness.
3. The correspondence of "behavior patterns" to specific unconscious defence mechanisms as well as to specific unconscious wishes.

Clinical analysis has proven time and again that chance plays no part in determining the choice of marriage partners. All of the stories promulgated in belles letters to the effect that a normal man becomes the prey of a seriously neurotic woman and, *vice versa*, that a normal woman is taken in by chance and without inner coöperation by a neurotic man, are not based on reality. Such assumptions are necessary in fiction for the furtherance of the plot. Real life is less romantic and more like a textbook of neuroses: *two* neurotics seek and find each other. The neurosis of the husband complements the neurosis of his wife, and *vice versa*. One could call the mechanism involved "unconscious synchronization of neurotic behavior patterns." To apply once more our simile, the marriage partners use each other to reel off their respective unconscious neurotic recordings.

In simple cases this fact is known even to the psychologically-untrained observer. Take, for example, an aggressive woman mistreating her husband, making fun of him in public in a derisive and humiliating way. We have no doubt—other possibilities excluded—that the husband who stands for this sort of behavior must be a weakling of the "milk toast" type. Seemingly, each gets what he wants: she, the pleasure of aggression; he, the pleasure of psychic masochism. Of course, the naive observer will simply say that the poor man had the *misfortune* of picking a shrew. Here the difference in interpretation enters in. The analyst will say that the man unconsciously wanted that "misfortune" and therefore contrived to get it. Furthermore, the words "shrew" and "weakling" or "sissy" are descriptive and not genetic terms. For instance, they do not explain how the aggressive woman happened to become so unpleasant or how the weak man happened to become a "she-" and not a "he-man." The surface description does not even hint at the genetic reasons. The difficulty in explaining this seemingly unreasonable choice increases if, for instance, we find the husband in our example constantly complaining

about his wife's mistreatment and sometimes even rowing violently with her, though he continues to stick to her. How are we to explain the slave-revolt, which obviously corresponds to a "defense mechanism" against his submission?

The decisive question is this: What is repeated and what constitutes genetically these patterns of behavior? Are only unconscious wishes involved or only unconscious defence mechanisms, or both, and if both are involved, what is their respective interrelation?

II. *Six Clinical Examples.* Six patients—3 couples—will be described for the purpose of showing the complicated web of "synchronization of neurotic pattern." All of these 6 patients were analyzed, and the material gathered is based on clinical observation. The summaries presented are sketchy of necessity, for the sake of brevity. For our purpose, *one* segment suffices.

Couple A. Mr. A. consulted me because of marital difficulties. He was a good-looking man of 43, with the charm and cynicism of a gamin. He explained his constant conflicts with his wife very simply: He was a "born bachelor," who did not marry, but was married by, his wife. He had warned her, but she had insisted, "and what can you do against a woman's determination?" Of women in general he spoke disparagingly: they were inferior creatures with no brain except for intrigue. I asked him of what his conflicts with his wife consisted. "Oh, she is terrible; she behaves like a governess, makes constant rows, is hysterical and overbearing." "How long did you know your wife before marrying her?" I wanted to know. "A year or so. But never mind, she changed completely. She told me then that she would give me back my freedom if our marriage didn't work. Well, it hasn't in 3 years, and now she refuses to divorce me." Asked what his wife had to complain about chiefly in him, he admitted that he "made some little mistakes." For instance, love letters from other women and his replies came "accidentally" into his wife's hands. He was, constantly reiterated a "born bachelor," and considered himself justified in having extramarital relations. Now, unfortunately, his wife had "material" against him, and that "complicated the matter."

A conversation with Mrs. A., a smart-looking woman appearing not more than 30 (although she was 40) revealed that she considered her husband "a terrible liar, in every respect unreliable, mercenary, and good-for-nothing." She denied that she had forced him to marry her and pointed out what a good influence she had had on him. She admitted that they fought, but shifted the responsibility completely to him. "I never made scenes before I discovered those letters, but afterward I wanted to know the truth." According to her, she quarreled only when her husband came out with "dirty lies." "If he would only confess I would forgive him, but he lies like hell." Asked why she insisted on having all of the details, she answered that she was afraid to meet people any longer, since she didn't know which were his girl friends and which knew about them, and was afraid of becoming a laughing stock. Full of fury, she accused her husband of being a "block of ice." "Of course he has the advantage, since when I react emotionally he calls me hysterical."

From the life story of Mr. A. one could gather that his beautiful mother had had the greatest influence on him, his father having been away often during his formative years. The patient emphasized the beauty of his mother, and it was evident that in his pseudo-charm he identified with her. Very soon it became apparent that he had unconsciously a strong feminine identification. This tendency he counteracted unconsciously with the pose of a Casanova and with

intellectual diaparagement of women. He gave, incidentally, as one of his reasons for allowing himself to "be married by" his wife his desire to break away from his "polysexual life." Without consistency, he stated on the other hand that he preferred his bachelor life. In any case, it became clear that all of the "bad qualities" he accused his wife of having (especially those of an overbearing governess) were exactly the ones which could fulfill his inner wish of being overwhelmed in a feminine way. Unconsciously there was in that layer a complete reversal for them of the man-wife attitude: He played inwardly the rôle of the woman; she, that of the man.

Interestingly enough, the patient was sexually uninterested in his wife. He attributed his lack of interest to two facts: first, that she was not his "type;" and, second, that her constant rows made sexuality impossible. The man was very potent but wanted to be seduced by his wife. She, however, played coy, and was rather passive in sex. One of the patient's chief objections against his wife was that, in a previous relation, she had actually seduced a man, a deed which she had mentioned to him as a practical joke when their acquaintance was slight. The patient dwelt constantly upon this deed, and more reproaches and more refusal in sex and money resulted. Despite the fact that his wife understood vaguely that her husband wanted to be seduced, she felt an inexplicable inhibition against "going back to the old times."

So far we see that the man wanted unconsciously to be overwhelmed in feminine identification—his wife was aggressive. He wanted, furthermore, constant hysterical rows, since they gave him the feeling of being mistreated—she also gave him that satisfaction. But all of these satisfactions were on the unconscious level. Consciously, he suffered "like a dog," to quote him. His wife provided for him only unconscious pleasures on a characterologic level; their sexual life was highly unsatisfactory. There the inner defence on his part set in. What he really wanted was not genital satisfaction; he had used this satisfaction, in previous relations, to a great degree to establish the alibi of being a "he-man." Basically his being mistreated satisfied his sexual needs in a masochistic way. But his constant complaints against his wife represented his unconscious defence. Even in this defence he smuggled in his old wishes; by refusing pseudo-aggressively sex and money, he provoked more aggression on her part and started once more the vicious circle of being unjustly treated.

The strange part in his unsolved œdipal relation was that his wife did not represent his "type," whereas women he had known in previous relations did. Obviously, this was because in marriage his defence had to go one step further in protecting him against his original wish, since it was easier to identify unconsciously his legitimate wife with his mother than girls of indifferent and transitory affairs. Consequently, the defence had to go one step further—avoidance of his "type." Even in his previous transitory affairs, however, it became obvious that our patient was not the great seducer, as he pretended to be. Quite the contrary; these women had to seduce him. By

means of his constant infidelity he tried in vain to prove to himself that he was, not passive, but aggressive toward women.

It might be asked how it happened that a man who had escaped marriage until he was 40 should finally have succumbed to it. The answer is that his original wariness against marriage represented an unconscious desire to avoid greater neurotic troubles, a form of self-preservation of the ego against greater inner danger. But, as is true of old bachelors when they marry, as they do often in their 40's, his neurosis increased with age, and he eventually bargained for greater trouble—and got it. His increasing craving for neurotic pleasure was also visible in his unconscious concocting of the situation in which his wife found the incriminating letters. Neurotics at that age want to repeat their neurotic repertoire 100%; innuendoes no longer satisfy them.

A few other facts are pertinent with regard to this patient. It was, of course, not true that his father played as unimportant a rôle in his life as he at first claimed. The patient was terrified of his father, and acquired thus strong castration fears which made it possible for him to shift from the identification with the father who possessed the mother ("positive" œdipus complex) to identification with the mother wanting to be overwhelmed by the father ("negative" œdipus). This feminine identification was repressed under the pressure of strong feeling of guilt. Interestingly, the psychopathic trends (lies, unreliability, etc.) could be traced to another identification, with the sister of his mother, who was the black sheep of the family, having various psychopathic symptoms and signs. His identification with her served different purposes: it satisfied the feminine trend in the patient, and could at the same time be used as an ironic weapon against the reproach of his inner conscience that he had such an identification, the unconscious reasoning being, "I cannot be a woman since all women are as impossible as my aunt." In identifying partially with his aunt, the patient also displayed aggression toward his family, thus once more making a play for his typical defence mechanism—pseudo-aggression.

Mrs. A.'s "rows" became so violent that she had to enter analysis, too. It developed that she had come from a family in which the mother was the predominating force. This woman had not only treated her child with coldness and reserve herself but had persuaded the child's father to do likewise. Whether this treatment was guided by some silly pedagogic idea as rationalization or was the mother's means of unburdening her own dislike of her husband was not clear. In any case, the child acquired a deep masochistic attachment to her mother and at the same time a strong aggression as inner defence. She displayed the latter tendency, living a polygamous life which was deeply offensive to her puritanical mother. Her dynamically-decisive masochistic tendency was expressed in the disappointments in life which she constantly brought about for herself. After many circuitous adventures, she married Mr. A., upon whom she unconsciously repeated the child-mother and mother-child situations. Mr. A. was as cold and detached as her mother, and her rows with him represented a futile attempt to get some reaction—even hatred! —from the pre-œdipal mother, her unconscious formula being, "I can't stand that coldness; even your hatred and anger would be more pleasant!" Consciously, of course, she wanted love; unconsciously she got what she wanted.

On another unconscious layer she was as cold and detached as Mr. A. was on the surface; strong narcissistic and unconsciously homosexual identifications were visible on both sides of the union. His unreliability was, by the way, a caricature of her own behavior "in the old days." This former period of polygamous tendencies she sought to counteract by a "model marriage," unfortunately with inadequate means. Unconsciously she knew only too well what to expect from a person of Mr. A.'s type. Not despite but *because* of her unconscious expectation of trouble did she choose him. For masochistic purposes, too, she confessed to him too much of her past.

Besides repeating the child-mother situation (playing again the unhappy child and forcing her husband into the rôle of her bad, cold mother) she also played the reverse situation, causing him to complain of her governess' characteristics.

As is true of all polygamous women who decide to make a break and become "respectable society," Mrs. A. overdid. Therefore she did not make use of her sexual experience and played virgin. Since Mr. A. wanted to be seduced, a stalemate resulted, in which both partners unconsciously enjoyed masochistically the rôle of "being unjustly treated," until their tendencies were solved in analysis.

Couple B. Mrs. B. entered analysis because of frigidity. She was married to a man who had lost sexual interest in her a few years after marriage. He claimed, however, that his attitude was the typical one of husbands, pointing out the fact of their 2 children to prove his potency. "In the past," his wife added ironically. He even went to the extent of compiling statistics on the subject, inquiring into the sex life of his friends. Since his friends were no less neurotic than he, his statistics were favorable to his contention. "And that is that," he concluded, and refused ever to discuss the subject further.

However, he had no objections to his wife's analysis, since he regarded her as "highly hysterical." Their marital life centered around one theme: *One of them was always being wronged.* Once the injustice was established, each marriage partner played the following unconscious game: He (or she) did not see that the provocation was his (or her) own. He (she) saw only the injustice, and started, seemingly in self-defence and in righteous indignation, to fight the other bitterly, with the result that both felt deeply hurt and enjoyed unconscious masochistic self-pity. This mechanism, repeatedly described by me[1,2] as the "mechanism of orality" and pathognomonic for a specific type of neurosis (neurosis with oral regression), is characterized by consciousness only of the defensive aggression and self-pity, with repression of awareness of initial provocation and masochistic self-enjoyment. The person suffering from such a neurosis is often considered "aggressive," whereas in reality his surface aggression is but a covering cloak for deep psychic masochism. Genetically, the mechanism has its start in early infancy, arising in the relation to, not the œdipal, but the pre-œdipal mother.

An example of the constant fights of this couple: She forced her husband to spend every Sunday with her mother, though she herself hated her, thus covering her masochistic attachment to her. The poor man had to drive the whole family to the country, miss his rest, swallow his fury, and above all, pretend to be very happy. Driving back once with his wife and mother-in-law in the back seat, he used the brakes too forcefully in stopping, jolting the two women disagreeably. Instantly his wife disparaged his driving ability. Her husband, not knowing that he had unconsciously provoked the scene by his unconscious pseudo-aggression, was helpless, felt unjustly treated, and accused his wife of malicious talkativeness.[3]

Another, less harmless example: By provoking the president of the large concern for which he worked, Mr. B. lost his position, the firm's laconic reason being, "Your personality does not fit into our organization." This was, incidentally, the reason for his wife's forcing him into analysis. He denied

that he had caused his dismissal himself, admitting only to a "perverted sense of humor." In reality, he had antagonized the president at every turn. In reviewing his life history, one could find many other examples of self-damagement of the same type.

It is impossible within the bounds of this paper to go into details about this couple, because to do so would necessitate a very technical description of "oral" neurosis in general and oral frigidity in particular, the most complicated of all types of frigidity.[4,8]

It was interesting to observe how the husband reacted to analysis. He regarded it for some time as an academic course, in which intellectual knowledge was to be acquired. His affective understanding was completely lacking. One day he said with disgust, "I see that if I continue analysis you will force me to have sexual relations with my wife, and that is exactly what I don't want." In other words, he wanted to "refuse," knowing inwardly only too well that his refusal provoked once more the masochistic cycle of counter-aggression on his wife's part.

This marriage lasted for 16 years on the basis of "I am unjustly treated," the initial provocation being nicely divided between the two partners.

COUPLE C. A 32 year old woman patient had been suffering from agoraphobia for 2 years, and entered analysis because of that symptom. For some months before the start of treatment, she had been unable to work, had given up going to her office, and had sat continually at home, where she felt less fear. To go out alone was impossible for her. She clung to her companion (either her fiancé or her sister, 20 years her senior) as if she were in imminent danger of death. Her fiancé was a gloomy person who looked upon his environment full of suspicion, whose facial expression showed dissatisfaction with everything and everyone. He gave the impression of inner fear, fury, and whimpering at once.

From the curriculum vitæ of the patient, who was quite pretty, though colorless and indifferent in appearance, we note: Her father died when she was 10 years old, but she was separated from him in her 7th year, when her parents divorced each other. She described him as an amiable man, though only one episode concerning him remained at first in her memory, that of being taken to his funeral but not crying. Later she recalled other things, which, connected with what her mother had told her of him, gave the following picture: Her father had been industrious and disinclined to drink until about his 50th year (when the patient was 5 or 6); then he underwent a change of character. He suddenly took to drink, became very noisy at home, and started exhibiting himself when drunk. Once in his drunken state he stripped himself naked before the children, and this, after 25 years of married life, served his wife as a signal to leave him, taking the children with her. The man lived 3 years more, took another wife, and saw his children only a few times thereafter. Evidently in order to paralyze his influence, his wife sent the small child to a convent school, to have "good morals" instilled in her. The year in the convent was, according to the patient, the unhappiest of her life. She lived in a constant state of fear, scarcely daring to go to the toilet. The nuns, evidently to prevent masturbation among the children, told them that the devil lurked there. In the course of a few months, the child was turned into a fearful, intimidated personality. By means of desperate pleading she persuaded her mother to take her away from the convent, but thereafter kept up a slight connection with it, attending sewing lessons there.

The patient described the further outward developments of her life as colorless. She was good at her studies and later entered a large concern, where

she had been employed for 12 years at the time of starting analysis. There she was regarded as a person who did not permit herself to be imposed upon and who often came into conflict with her superiors, especially her immediate boss, whom she despised.

The patient could not recall her childhood, and claimed that her first memories were of her 8th year. She denied childhood masturbation, but remembered masturbating in puberty, though she could not recall the fantasies which had accompanied it. When she was 20, she became acquainted with a man considerably older than herself, who suffered from a serious case of tuberculosis and was at times unable to work. She had a sexual relation with this man for 7 years. She described this relation as a very close one, in which she enjoyed complete orgasm. After great conflicts with her mother, an aggressive hypochondriac, who objected to her choice of fiancé because of his illness, she met him outside of her home. Their relationship continued to be good, with great self-sacrifice in nursing him on her part, *until the man was cured of his tuberculosis, when the patient suddenly abandoned him*. According to her rationalization, she realized, as time went on, that her mother had been right in trying to talk her into giving him up because of his illness.

One would expect the patient, having broken off her first engagement because of her fiancé's tuberculous condition, to be more careful in her choice of a second fiancé. By a curious "chance," however, her second betrothed, the man who accompanied her to her analytic appointments and who has been described before, *also suffered from a severe case of tuberculosis*.

The patient's first symptoms of agoraphobia appeared during the last months of her relationship with her first fiancé. She began the second relationship in a period when her symptoms were becoming stronger, and felt, even after the first sexual contact with him, that he was not "the right man" for her. According to her, all tenderness was lacking and he was needlessly and pathologically jealous of her. His jealousy was peculiar: On the one hand he tortured her with accusations of faithlessness; on the other hand he demanded that she be unfaithful to him in the realm of fantasy. He was able to have sexual intercourse only under the following conditions: She must describe to him, *during intercourse*, her intercourse with other men. Since the patient could oblige only with 1 man, her partner had to be contented with stories of imaginary love-affairs. He made her describe in a very realistic manner just how other men conducted themselves during intercourse, what they said, how they reacted, etc. If she refused to do so, the man was impotent or was unable to reach ejaculation during coitus. He demanded further that, in telling the stories, she make use of "popular designations," that is, obscene words. The patient was indignant at her betrothed's requests. Her agoraphobia was setting in more strongly and her sexual desires were diminishing, so that intercourse between the pair became infrequent, and was accompanied by more and more antipathy on her part.

It is impossible to give in this paper the details of the patient's analysis; this has been done elsewhere.[5] Nor is it feasible to enumerate the complicated reasons for this symptom agoraphobia; in the original report 13 determinants are worked out. For our purposes it suffices to state the reasons for the patient's strange choice of fiancé. At the time when her father began to drink, the child was at the peak of her œdipus conflict. During analysis she suddenly remembered that she was the only one who could "tame" him in his drunken state, and that her mother, at a loss to deal with the raving, drunken man, would send her right into his room. This agreed with her mother's report that she was her father's favorite. What took place between father and daughter was at first difficult to reconstruct. There was no proof that the man sexually misused the child. Probably he

exhibited himself and urinated before her. However, we know that for the unconscious, wish and reality have the same psychic value. The fact remains that the child, while in the first critical blossoming of the œdipus complex, found an opportunity to take over the rôle of her mother, indeed, was actually pushed into this rôle by her mother. The patient, however, acquired an exorbitant unconscious sense of guilt, with consequent desire for punishment; for, as may be imagined, her mother's permission went only so far as taking care of the father, not to the extent of realization of the œdipus fantasies. The child unconsciously interpreted her mother's desertion of her father and placing of her in a convent school as punishment. To this was added feeling of guilt because of masturbation.

The conundrum presented by her choice of first fiancé and subsequent leaving of him becomes unraveled if we consider that the patient unconsciously identified him with her father. Her mother's violent effort to make her give up this man was the signal for her neurosis, which had been present since childhood, to become manifest. Her mother's advice mobilized the girl's entire repressed sense of guilt and desire for punishment. In penance she gave up the man, in doing so identifying with her mother, who had given up her husband. The grotesque fact that the patient gave up her first fiancé just as he became cured, only to take up the rôle of nurse to another sick man, can be explained on the basis that for her *illness of the man was a necessary condition for every sexual relationship*, because in her childhood her unconscious œdipus wishes had been permitted only when accompanied by the inner excuse, "I am taking care of my drunken (sick) father." The patient left her first fiancé, *not in spite of but because of his return to health*, when the guilt-relieving fact existed no longer. She then again became attached to a man who fulfilled her inner prerequisite. She stuck to him in spite of her feeling that he was "not the right one" for her and in spite of his repugnant demands *because* at this stage in her neurosis he took over the rôle of *executor of her desire for punishment*, this extremely neurotic man being well suited to his rôle of jailer.

There were also other factors which contributed to her toleration of her second fiancé. She was herself an exquisite exhibitionist and voyeur, as was visible in her symptom of street-fear. Her main fear, of fainting on the street and thus making a spectacle of herself, especially indicated these traits. Of course, her conflict with her fiancé concerning scopophilia came to the fore under defensive disguise (she apparently objected strongly to his visualizing of sexual scenes between her and other men). On the other hand, the man complained constantly about her own scopophilia. For instance, one morning as they were both going up in the elevator of the building in which they were employed, she opened her coat and noticed that she had "forgotten" to put on a blouse. She reacted to the discovery with hearty laughter, he with an outbreak of rage. On another occasion she injured her knee and displayed her injury quite freely in the office. Occasionally she would fix her eyes on the genital region of men while riding in the streetcar, denying it when her fiancé became enraged.

When the patient's symptoms had subsided considerably and she was approaching cure, her fiancé demanded analysis so urgently that he could not be put off any longer. His conscious reason for entering analysis was his masturbation, which, strangely enough, was accompanied by conscious fantasies of watching his parents have intercourse. His real, unconscious reason for demanding analysis was scopophilia: He believed that something mysterious was going on between his fiancé and the physician, for instance, that she was acquiring some forbidden knowledge which he wanted, too. He simply projected his childhood voyeurism regarding his parents on to his fiancé and the physician. The problem arose as to why in his case the œdipal fantasy of observing the coitus of the parents (he could remember seeing this coitus) had remained conscious and had not been repressed as usual. The answer was that he unconsciously identified with his mother, and as a defence against his feminine wishes, built up his "he-man" attitude. And even this defense was possible only under the disguise that not he but another man had intercourse. Hence his conscious demand that his partner relate her previous sexual experiences. He performed, so to speak, "incognito" or "anonymous" coitus.* His unconscious reasoning was, "It is not I, but someone else, who does these forbidden things, and since I am neither doing nor saying anything, I cannot be held in any way responsible." So the girl, not he, had to use obscene language. His neurotic jealousy (defence against unconscious homosexuality) also indicated his feminine identification.

The strongest link between the 2 patients was the disguised scopophilia. An additional link was her desire to be mistreated and tormented because of unconscious guilt and his ability to fulfill her desire in his frantic attempt to provide an alibi for his unconscious feminine identification *via* pseudo-aggression. In humiliating the girl by forcing her to use obscene language he worked in the same direction.

Conclusions. "Synchronization of neurotic behavior patterns" refers to a married couple's mutual projection of their respective neurotic tendencies upon each other. It is adopted as a compromise of unconscious wishes and defence mechanisms. The contents of the two neuroses thus lived out are by no means simple unconscious wish fulfilments. Quite the contrary, *the stress lies often in the unconscious defence.* The neurotic stability of these relations depends on the segment of projection; the more nearly the two neurotic tangents meet, the stronger the bond. Cases 1 and 2 remained united. The woman of Case 3 gave up her fiancé when his main function—that of executor of her unconscious guilt feeling—had been made superfluous by analysis. In evaluating the stability of such relations, one must also take into account the great tendency toward *narcissistic self-duplication* in the marriage relation. Even partially successful analysis often does not break up such marriages: Narcissism and remnants of the respective neurosis rationalized with external difficulties

* For details see previous publications.[6,7]

accounts for this fact. Sometimes it is possible to place the old relation on a more normal basis.

The irony in the "synchronization of neurotic behavior patterns" is that the accompanying music is a cacophony of shouts, fights, complaints, reproaches, and tears. Whereas 2 normal persons with similar likes and dislikes achieve some degree of harmony, 2 neurotics with similar "likes" and "dislikes" show on the surface only lack of harmony. The difference is exactly the difference between conscious and unconscious pleasure. The latter, however, must be covered up, and appears only under a palimpsest. Whoever doubts the fact that behind that superficial disharmony lie deep unconscious pleasure and equally satisfying appeasement of the inner conscience in the form of defence mechanisms, should ask himself why these constantly unhappy people, who seemingly hate each other, stick together. Onlookers often venture pessimistic prognoses concerning the future of such marriages. Their prognosis only too often turns out to be erroneous—the glue of neurosis holds such marriages together.

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ATRIAL SEPTAL DEFECT

Study of Hemodynamics by the Technique of Right Heart Catheterization*†

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Although during recent years the clinical and roentgenologic picture of cardiac septal defects has become more clearly defined,[2,5,12]

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† Part of this material was presented at a meeting of the Mid-Western Section of the American Federation for Clinical Research in Chicago, November 2, 1944.

little knowledge has been gained regarding the altered cardiovascular dynamics in this condition. It is usually stated that blood flows through the atrial septal defect from left to right. If this occurs, the right ventricle must pump not only the normal quota of blood, but in addition that blood which leaks through the septal defect. The evidences of hypertrophy of the right ventricle and the prominence of the pulmonary artery found in patients with atrial septal defect are cited in support of such a belief. The development of the technique of right heart catheterization has allowed us to test this hypothesis and to demonstrate that arterial (oxygenated) blood actually does enter the right atrium in patients with the clinical picture of atrial septal defect. It has also permitted us to exclude the diagnosis of defect in patients with hypertrophy of the right ventricle and prominence of the pulmonary artery due to other causes, by demonstrating that oxygenated blood was not entering the right atrium.

This paper reports observations on 4 patients with the clinical picture of an atrial septal defect in whom oxygenated blood was entering the right atrium.

Methods. The method of catheterization of the heart and great vessels utilized in these studies is only slightly modified from that reported by Cournand and his colleagues.[7] The median basilic vein of either arm was exposed through a small incision in the antecubital space. The vein was isolated and a small nick made in its wall. A special radiopaque ureteral type catheter* (No. 8 or 9) with an angulated tip was then introduced into the vein and passed up the venous channels under fluoroscopic guidance. The catheter was first passed up the arm veins and through the superior vena cava into the right atrium, thence into the inferior vena cava for several centimeters below its entrance into the heart. Throughout the procedure a very slow drip of physiologic saline solution was maintained through the catheter to prevent clotting of blood in its lumen. Before blood samples were drawn for analysis, several cubic centimeters of blood were withdrawn through the catheter and discarded. This avoided any dilution of the sample by the saline contained within the catheter. Samples were then withdrawn, collected under oil, and analyzed for oxygen content by the method of Van Slyke.[10] Only duplicate analyses, which checked within 0.1 volume %, were accepted as satisfactory. After samples were obtained from the inferior vena cava, the catheter tip was withdrawn to the right atrium and finally to the superior vena cava. Specimens for oxygen analysis were obtained from these locations also. In 3 patients the catheter was passed into the right ventricle and in another it apparently passed through the septal defect into the left atrium. Arterial blood for analysis was collected through an inlying needle in the femoral artery, which had previously been well novocainized. The arterial pressure was measured directly by the method of Hamilton[8] and the pressure in the chambers of the heart by either the Hamilton manometer or by a simple saline manometer of the type commonly used for venous pressure measurements. The level of the right atrium was considered to be 5 cm. below the 4th costochondral junction. Oxygen consumption was determined by collecting a sample of expired air in a Douglas bag and analyzing its content by the method of Haldane.[10] From these data the cardiac output was calculated utilizing the Fick principle.

The safety and utility of the methods used in this study have been demonstrated by their extensive use in several laboratories.[7,9,14] In this laboratory over 420 catheterizations have been carried out without any serious untoward effects. Local venous thrombosis at the site of the incision of the vein may

* Obtained from the U. S. Catheter and Instrument Company, Glenn Falls, N. Y.

occur, but the vein is usually recanalized in 2 to 3 weeks, and several subjects have had multiple catheterizations carried out. Considerable care and gentleness in manipulation are required to obtain satisfactory results. If adequate novocainization is maintained, observation of the type recorded here may be made with the patient quiet and relaxed.

Observations. Patients 1 through 4 were subjects who had no evidence of congenital heart disease. Patients 5 through 8 were diagnosed clinically as having an atrial septal defect. Table 1 is a summary of the data obtained in the study of these patients.

The table contains two values for the cardiac index (the cardiac output per sq. meter of body surface). The first is that calculated, as is usually done, utilizing a sample of blood from the right atrium to determine the oxygen content of mixed venous blood. The second value was calculated using the average oxygen content of the blood from the superior and inferior cavæ as the oxygen content of mixed venous blood. In the patients without evidence of congenital heart disease the cardiac indices obtained by the 2 methods agreed very well because the blood in the right atrium was a mixture of that from the superior and inferior cavæ. In the patients with the clinical picture of atrial septal defect the 2 methods gave very different results. The finding that the oxygen content of the atrial blood was higher than that of the blood from the superior and inferior cavæ demonstrated that oxygenated blood, as well as the blood from the cavæ, was entering the right atrium.

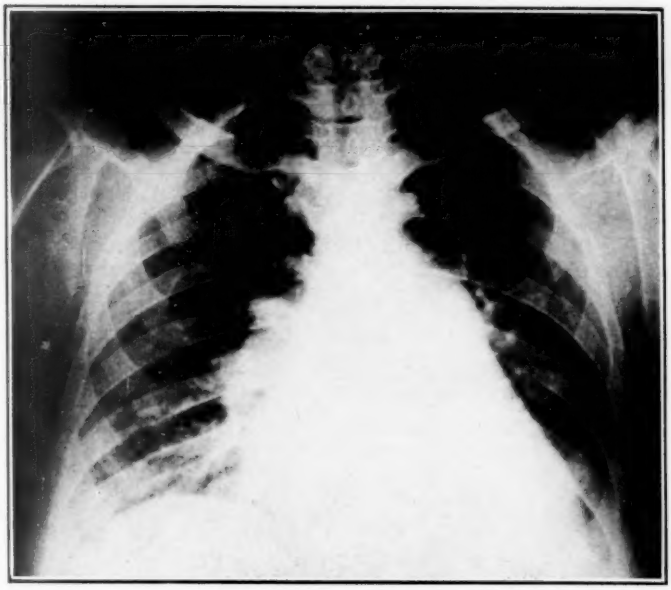
The clinical data on Patients 5 through 8 follow:

PATIENT 5. A 32 year old colored woman was admitted to Grady Hospital in March, 1944 because of increasing dyspnea of 2 years duration, which had finally reached the stage of orthopnea. Examination on admission to the hospital revealed enlargement of the heart to the left in the 3rd to 5th intercostal spaces, a very loud harsh systolic murmur over the entire precordium, maximal in the 2nd intercostal space just to the left of the sternum. Over this area there was a distinct systolic thrill. There was no diastolic murmur. The pulmonic second sound was markedly accentuated. There was moderate edema of the lower extremities. Roentgen ray examination (Fig. 1) at this time revealed that the heart was markedly enlarged, chiefly to the left (total transverse diameter of the heart 15.9 cm., total transverse diameter of the chest 26.6 cm.). The diaphragms were somewhat elevated. The aortic knob appeared hypoplastic, and the left heart border below the aortic knob bulged outward. Moderate dilatation and striking pulsation of the major branches of the pulmonary artery were noted. The anterior bulging of the heart in the left anterior oblique position was interpreted as enlargement of the right heart chambers. The left atrium was not dilated. An electrocardiogram showed only a tendency toward right axis deviation.

After remaining in bed for several days and receiving digitalis and diuretics, the condition of the patient improved. It was noted that the murmur had diminished considerably in intensity and harshness. At this time the studies summarized in Tables 1 and 2 were performed. In an effort to study the factors influencing the flow of blood through the septal defect, the right atrial pressure was elevated by means of a rapid intravenous infusion of physiologic saline solution. This produced no significant change in arterial oxygen saturation, which might have been expected if the elevated right atrial pressure had caused blood to be shunted from the right side of the heart to the left side. Placing the patient in the left lateral position with the head down and the intravenous injection of 0.16 mg. of epinephrine also failed to produce change in arterial oxygen saturation.

Reëxamination of the heart by Roentgen ray at this time (2 weeks after the first examination) showed a decrease in the transverse diameter of the heart (total transverse diameter of the heart 12.7 cm., total transverse diameter of the chest 24.3 cm.). There was no change in the appearance of the pulmonary artery.

On most recent examination (February, 1945) the patient's condition and physical findings were essentially unchanged.



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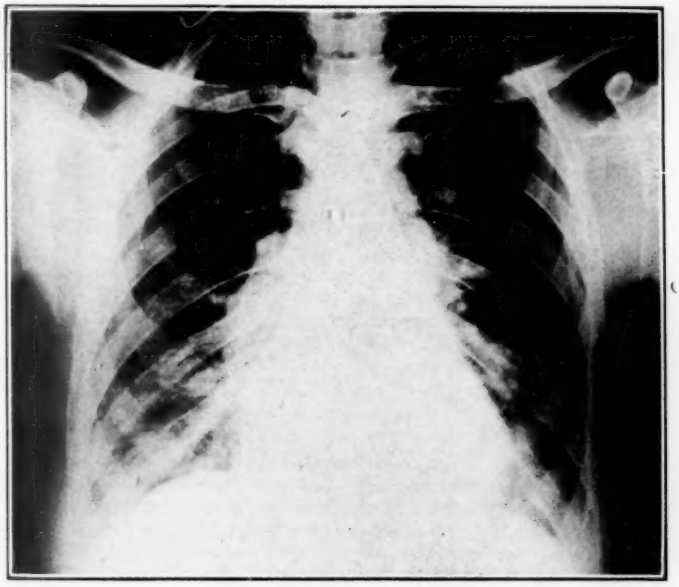

B

FIG. 1.—Teleoroentgenograms of the chest of Patient 5. *A*, On admission to the hospital. *B*, Two weeks later.

The *diagnosis* of an uncomplicated atrial septal defect was made.

PATIENT 6. A 68 year old colored female was admitted to Grady Hospital in 1941 because of symptoms related to diabetes mellitus. Although she had no symptoms referable to the cardiovascular system, the heart was enlarged and there was a systolic murmur best heard over the 3rd and 4th left intercostal spaces near the sternal border. The pulmonic sound was accentuated. Roentgen examination revealed that the heart was markedly enlarged in the transverse diameter, chiefly to the left side (total transverse diameter of the heart 15.9 cm., total transverse diameter of the chest 25.6 cm.). The aorta was somewhat elongated and the aortic knob was prominent. The pulmonary artery appeared markedly dilated and showed on fluoroscopy considerable expansile pulsation. There was no enlargement of the left atrium. The right chambers of the heart were found to be enlarged on fluoroscopic examination in the oblique positions.

TABLE 1.—SUMMARY OF OBSERVATIONS ON PATIENTS WITH AND WITHOUT ATRIAL SEPTAL DEFECT

Patient and diagnosis	Oxygen content of blood (vols. %)						Oxygen consumption (cc. per min. per sq. m.)	Cardiac index* (liters per min. per sq. m.)	
	Superior vena cava	Right atrium	Inferior vena cava	Right ventricle	Left atrium	Femoral artery		A	B
1—Bronchogenic carcinoma, hypochromic anemia	6.9	6.5	5.9	..	..	10.8	179	4.2	4.2
2—Normal	16.5	16.4	17.2	..	..	19.5	123	4.0	4.5
3—Hypertensive vascular disease, cerebral thrombosis	14.4	14.2	15.0						
4—Rheumatic heart disease with mitral stenosis, anemia	8.2	6.3	6.8	..	..	13.7	165	2.2	2.7
Average—Patients without atrial septal defect	11.5	10.9	11.2	..	..	14.7	156	3.5	3.8
5—Atrial septal defect	10.4	12.1	9.5	12.8	..	14.1	116	5.8	2.8
6—Atrial septal defect	10.1	13.7	12.0	14.1	..	14.8	136	12.4	3.6
7—Atrial septal defect	13.4	16.9	13.4	..	18.8	18.7	154	8.5	2.9
Average—Patients with uncomplicated atrial septal defect	11.3	14.2	11.6	..	..	15.9	135	8.9	3.1
8—Atrial septal defect with pulmonary vascular disease	7.9	12.4	...	12.1	..	13.0	181	30.0	3.5

* A—Oxygen content of right heart blood used in calculating cardiac output.

* B—Average content of superior and inferior vena caval blood used in calculating cardiac output.

TABLE 2.—ADDITIONAL HEMODYNAMIC DATA ON PATIENTS WITH ATRIAL SEPTAL DEFECT

Patient	Arterial oxygen saturation (%)	Pressure			
		Right atrial (mm. water)	Right ventricular	Femoral arterial	
				Syst./Diast.	Mean
				Mm. Hg	
5	92	0	40	122/60	81
6	88	60	41	140/60	87
7	91	15	..	115/60	76
8	67	180	112–146	151–166/91	111

Reëxamination after 18 days of hospitalization disclosed a striking diminution in the transverse diameter of the heart (total transverse diameter of the heart 12.9 cm., total transverse diameter of the chest 25 cm.). There was no change observed in the appearance of the pulmonary artery or aorta.

The patient was readmitted in April, 1944 for special study. There were still no complaints referable to the cardiovascular system. The physical findings were the same as previously noted. Fluroscopic and radiographic studies showed no significant change since the previous examination. An electrocardiogram showed right axis deviation. The results of studies at

this time are recorded in Tables 1 and 2. With the patient tilted to the head down position there was no significant change in arterial oxygen saturation.

The *diagnosis* of an uncomplicated atrial septal defect was made.

PATIENT 7. A 44 year old white male was admitted to Grady Hospital in March, 1944 for special study of the cardiovascular system. He had experienced dyspnea on exertion for the past 9 years, and occasional attacks of paroxysmal nocturnal dyspnea and orthopnea for the past 3 years.

The heart was found to be enlarged to the left in the 3rd through the 6th intercostal spaces. The rhythm was regular; a low pitched, soft systolic murmur was heard over the 3rd and 4th intercostal spaces. The pulmonic second sound was greater than the aortic second sound. No diastolic murmur was heard. No other abnormalities were detected.

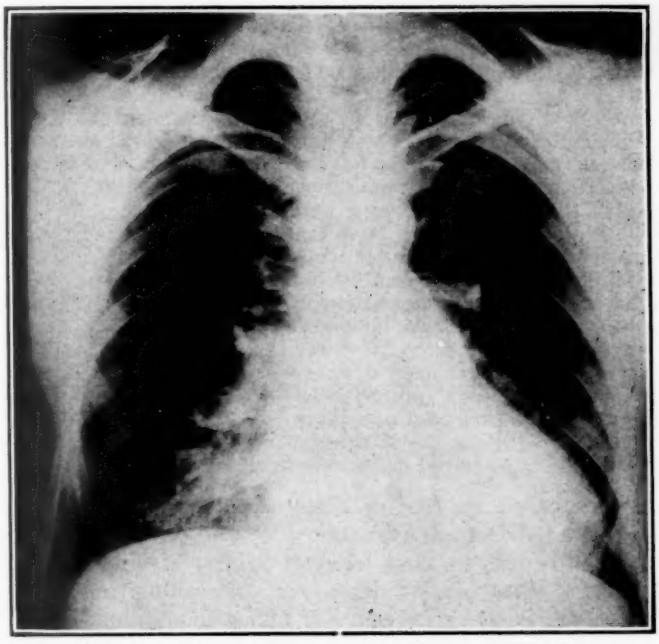

FIG. 2.—Teleoroentgenogram of the chest of Patient 7.

Roentgen examination (Fig. 2) revealed enlargement of the cardiac silhouette toward the left side (total transverse diameter of the heart 15.2 cm., total transverse diameter of the chest 29.8 cm.). The aortic knob was slightly shortened. The major branches of the pulmonary artery revealed only slight accentuation and did not show any unusual pulsation. Fluoroscopically enlargement of both ventricles was demonstrated. There was no enlargement of the left atrium observed. An electrocardiogram showed only right axis deviation.

The results of the special studies on the circulation are recorded in Tables 1 and 2. On 2 occasions the tip of the catheter was advanced so that it first passed to the left from its position in the right atrium, and then headward to form a reversed J shape on fluoroscopic visualization. The pressure at this time was found to be from 0 to 15 mm. of water, using the same reference point as previously, while that in the right atrium was −10 mm. of water. On being tilted in the head down position the arterial blood remained normally saturated with oxygen.

The *diagnosis* of an uncomplicated atrial septal defect was made.

PATIENT 8.* A 39 year old white male was admitted to Grady Hospital in February, 1945. At the age of 12 he had been told that he had a heart murmur. There was no history of rheumatic fever. At the age of about 26 slight dyspnea on exertion first appeared. This had become progressively more severe and for the past 7 years he had been having occasional attacks of nocturnal dyspnea. One year before admission his physician performed several phlebotomies because of polycythemia.

On admission to the hospital he appeared to be slightly dyspneic while lying quietly in bed. There was moderate cyanosis. The heart was markedly enlarged to the left and right. There was a loud rough systolic murmur over the entire precordium, heard best at the apex and almost completely replacing the first heart sound. At times a low-pitched, rumbling, late diastolic murmur was audible at the apex. The pulmonic second sound was accentuated and was louder than the aortic. The rhythm was regular. There was no clubbing of the extremities.

Roentgenologic examination revealed that the heart was markedly enlarged (total transverse diameter of heart 20.2 cm., total transverse diameter of chest 28.1 cm.). The right ventricle was quite prominent and its pulsations were of increased amplitude. The aortic knob appeared shortened. The pulmonary artery segment of the left heart border was markedly protruding and its pulsations were more prominent than usual. The large intrapulmonary branches of the pulmonary artery were dilated. Some of these branches showed a moderately increased pulsation, whereas others had practically no pulsatory volume changes. The left atrium was questionably enlarged. There was no definite intracardiac calcification demonstrated.

The diaphragms were low in position and showed normal motility. Fibrosis was seen throughout both lower lung fields.

An electrocardiogram showed evidence of marked right axis deviation. Special studies on the circulatory dynamics are summarized in Tables 1 and 2. In addition, the arterial O_2 saturation rose from a control level of 67 to 88% after the patient breathed pure oxygen through a B. L. B. mask for 10 minutes.

The *diagnosis* of atrial septal defect complicated by pulmonary arterial disease and possibly by mitral stenosis (Lutembacher syndrome) was made.

Discussion. Detailed studies of the clinical and pathologic picture of atrial septal defect are available.[2,5,12] The patients reported here fit well in all respects. They were all adults, varying from 32 to 71 years in age. One patient denied any symptoms referable to the cardiovascular system (Patient 6). The remaining 3 had noted dyspnea and palpitation on exertion for years and, by the time they were seen in the hospital, had some evidence of congestive heart failure. All 4 patients had physical signs denoting cardiac enlargement. All had a systolic murmur heard along the left border of the sternum from the 2nd to the 5th intercostal spaces. We were impressed by the variation in intensity and quality of this murmur. After prolonged bed rest it was often faint and only moderately harsh, but after even mild exercise it would become much louder and harsher, often accompanied by a thrill. In all patients the pulmonic second sound appeared to be accentuated. Only in 1, Patient 8, was a diastolic murmur audible. This same patient was the only one exhibiting cyanosis, and in this instance there was evidence of complicating pulmonary arterial disease. All patients showed evidence of right axis deviation in their electrocardiographic tracings.

* This patient was kindly referred to us by Dr. J. C. Massee for the special studies reported here.

The roentgenologic findings in Patients 5 and 6 correspond to the classical description of atrial septal defect given by Roesler.[12,13] The characteristic features are marked dilatation and increased pulsation of the pulmonary artery, shortening of the aortic knob and marked enlargement of the right heart chambers. Any of these features may be less pronounced or even absent. Thus in Case 7 the pulmonary artery was only slightly prominent and did not show remarkable pulsation (Fig. 2). On the other hand, one or more of these characteristic roentgenologic signs may be encountered in other forms of heart disease, such as patent ductus arteriosus, cor pulmonale, and rheumatic heart disease. It is for this reason that corroborative clinical and laboratory evidence is necessary for the diagnosis of atrial septal defect.

Roesler[12] differentiating atrial septal defect and patent ductus arteriosus, states that the heart is generally much larger in the former. A similar opinion with regard to cor pulmonale is expressed by Rigler and Hallock,[10] though these authors believe that the distinction between these two conditions depends largely on history and physical signs. It was striking to us that the transverse diameter of the heart in Patients 5 and 6 was markedly and rapidly reduced after treatment of the congestive failure (Fig. 1). Therefore, the characteristic "large" heart was no longer an important feature in differential diagnosis. The concept of the large heart in atrial septal defect is probably based on observations of patients in cardiac failure and on autopsy reports. With newer diagnostic methods it is likely that atrial septal defects may be recognized in patients with little or no cardiac enlargement.

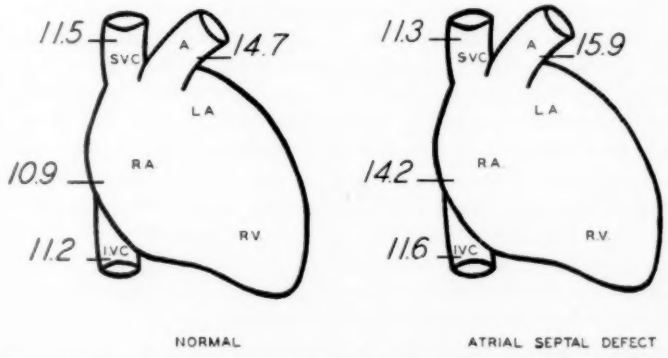

FIG. 3.—Diagram representing a summary of observations on 3 patients with uncomplicated atrial septal defect and 4 patients without evidence of septal defects. The approximate site of obtaining the various specimens is shown by the following: S.V.C., superior vena cava; R.A., right atrium; I.V.C., inferior vena cava; L.A., left atrium; R.V., right ventricle; A., arterial.

In recent years angiocardiography has contributed a great deal to the roentgenologic analysis of cardiac configuration and determination of the size of single heart chambers. The interatrial shunt is, however, only occasionally demonstrated with angiocardiography, and even then with difficulty and not unequivocally.[15] The chief difficulties

are said to be slow injection of the radiopaque material, passage of the injected material into the inferior vena cava, and transient increase in right atrial pressure stopping or reversing the flow through the defect. The latter effect may indeed become helpful in that it will give evidence of the presence of the defect.

The results of the analysis of the oxygen content of vena caval and atrial bloods in Subjects 1, 2, 3 and 4 are essentially what one would expect in a person with a normal heart (Fig. 3). None of these patients had clinical evidence suggesting atrial septal defect. It is to be noted that the average value for the oxygen content of right atrial blood in these patients was 10.9 volumes %, in contrast to 11.5 and 11.2 volumes % for the superior and inferior vena cava respectively. We feel that inadequacy in sampling of the inferior vena caval blood best explains why this value for atrial blood appears to be slightly lower than one would theoretically anticipate. The hepatic veins, which normally carry a rather large amount of quite deoxygenated blood,[17] empty into the inferior vena cava at a point so close to the heart that when the catheter tip is in a position definitely within the inferior cava, it is possibly below the point of drainage of the hepatic veins. As a matter of fact, at times the hepatic veins may empty directly into the right atrium. This position of the catheter below the hepatic veins would fail to take into account the large amount of blood with a low oxygen content coming from the liver. Thus one is not surprised that the actual value obtained on atrial blood may be slightly lower than that from either vena cava. Another potential source of error in sampling of the inferior vena cava is the existence of streams of blood with a high oxygen content coming from the renal circulation.[18]

In Patients 5, 6, 7 and 8 (Fig. 3) there was clinical evidence suggesting the diagnosis of atrial septal defect. The average oxygen content of the right atrial blood obtained from the 3 patients with apparently uncomplicated atrial septal defect was 14.2 volumes % in contrast to values of 11.3 and 11.6 for blood obtained from the superior and inferior vena cava respectively. This demonstrated that oxygenated blood was actually entering the right atrium, presumably passing from the left atrium to the right atrium through the septal defect. The fact that blood obtained from the right ventricle had essentially the same oxygen content as that from the right atrium gave definite proof that there was a real shunt and indicated that the results obtained on atrial blood were not due to passage of the catheter partially through the septal defect. In Patient 7 the tip of the catheter apparently did pass through the septal defect into the left atrium. Blood obtained from this site had the same oxygen content as that of a simultaneously obtained specimen from the femoral artery.

A possible confusing factor in these studies is the uncommon anomaly in which one or more pulmonary veins empty into the right side of the heart rather than into the left side as they normally do.[1,4] Most frequently such anomalous channels empty into the superior vena cava and would, therefore, be distinguishable from atrial septal defect.

If the rare situation did exist when the pulmonary vein did empty into the right atrium, there would be blood oxygen changes identical to those seen in atrial septal defect.

The cardiac output values are of interest. Since, in the presence of atrial septal defect, much of the output of the right side of the heart returns to the right side of the heart, it is obvious that the output of the 2 ventricles is not equal. If the Fick principle is utilized in the usual way in patients with atrial septal defect, the value obtained is that for the output of the right ventricle. If, on the other hand, a value for oxygen content of mixed venous blood is obtained from the average of the oxygen content of blood from the 2 venæ cavæ, we obtain an approximate value for the output of the left ventricle (Table 1). It may be noted that the values obtained for the output of the left ventricle by such means are in the range of normal subjects obtained by the catheter method.[7] These data give some idea of the functional size of the shunt. In all of our patients the output of the right ventricle was at least twice that of the left. This is an interesting datum when one speculates as to the various factors which control the output of the heart. Although the atrial pressure in the two sides of the heart (*vide infra*) is not greatly different, one is pumping over twice as much blood as the other. A satisfactory explanation for the left right shunt has not been offered.

It is usually stated that the blood flows from the left side of the heart to the right because of the difference in pressure within the two chambers. In Patient 7, where the catheter apparently entered the left atrium, the pressure as measured in the two atria appeared to differ by 10 to 25 mm. of saline. Accurate measurements of this difference are almost impossible because of the velocity of flow from one to the other and changes produced by respiration. Uhley[16] has suggested that the blood flows from the left atrium to the right because of the relative position of the two chambers. He points out that the left atrium is more cephalad than the right with the patient in the upright position. The plane that separates them is horizontal, rather than vertical as is usually supposed. He also notes that most of the difficulty in patients with this type of defect comes in adult life, when the patient is more often in the erect position. We have investigated Uhley's suggestion by attempting to reverse the flow through the defect by standing the patient in the head down position. If the flow from left to right is actually a result of gravity reversing the position of the body should reverse the flow by placing the right atrium above the left. This was tried in 3 patients by supporting them in the head down position. We failed to find any change in arterial oxygen saturation while in this position. If right to left flow had occurred, venous blood would have been shunted into the arterial system, with subsequent diminution in arterial oxygen saturation.

In 3 patients, pressure tracings were obtained from the right ventricle. In 2 instances these were slightly, but probably not significantly, higher than similar tracings obtained in normal subjects in this laboratory[13] and elsewhere.[16] These pressure measurements,

plus those from the right atrium, failed to give any evidence of insufficiency of the tricuspid value. In Patient 8 the systolic pressure in the right ventricle varied between 112 and 146 mm. Hg. In this patient there was also marked arterial oxygen unsaturation, which was relieved to a large extent when the patient breathed pure oxygen. This observation indicated that there was difficulty in oxygenating blood in the lung, rather than an intracardiac shunt, as the cause of the arterial unsaturation. It has been noted previously that atrial septal defect may be complicated by sclerotic changes and thrombosis of the pulmonary vessels.[2,5] It was felt that probably Patient 8 had such changes in his pulmonary vessels.

The elevated right ventricular pressure may, however, be due to other factors. In patients with emphysema and pulmonary fibrosis the right ventricular pressure has been found to be elevated.[13,16] It has also been noted that in patients with mitral stenosis the right ventricular pressure may be abnormally high.[13,16]

Having demonstrated that a left right shunt occurred in patients with the usual clinical picture of atrial septal defect, we have utilized the catheter technique to exclude the possibility of this lesion in patients with hypertrophy of the right ventricle and prominence of the pulmonary artery due to other causes, such as cor pulmonale or pulmonic stenosis.

It would be of interest to apply this method of study in patients with ventricular septal defect. In patients with an atrial septal defect the right ventricular and right atrial blood have essentially the same oxygen content. In the presence of a ventricular defect one would expect that the right ventricular blood would have a higher oxygen content than the right atrial blood because of admixture with oxygenated blood from the left ventricle.

Summary and Conclusions. Four patients with clinical evidence suggesting the diagnosis of atrial septal defect have been studied, utilizing the technique of right heart catheterization. The clinical and roentgenologic picture presented by these patients did not differ significantly from that described by others.

The oxygen content of right atrial blood in normal subjects might be expected to be somewhere between the values found for superior and inferior vena cava blood, since blood in the right atrium is a mixture of blood from the venæ cavæ. This has been verified in 4 normal subjects. On the contrary, right atrial blood from the 4 patients with atrial septal defect had a much higher oxygen content than blood from either the superior or inferior vena cava. This indicated actual shunting of arterial (oxygenated) blood from the left atrium to the right atrium. In 1 patient, the catheter apparently passed through the septal defect into the left atrium and the blood obtained had the same oxygen content as arterial blood.

The right ventricular pressure in 2 patients with uncomplicated atrial septal defect was 40 and 41 mm. Hg. This is probably not significantly above normal. In a 3rd it varied from 112 to 146 mm. Hg. In this patient there was additional evidence suggesting the presence of pulmonary arterial disease.

In all patients with a septal defect the output of the right ventricle appeared to be at least twice that of the left ventricle.

The catheter technique offers a safe and useful method of differentiating atrial septal defect from other causes of hypertrophy of the right ventricle and prominence of the pulmonary artery.

The authors are indebted to Dr. E. A. Stead, Jr., for his advice and help in this work. Miss Eloise Cavin, Miss Maurine Giese, Mrs. Jane Bailey and Miss Lois Jackson gave valuable technical assistance.

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IDIOPATHIC (?) HYPOPROTHROMBINEMIA

REPORT OF A CASE

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We have observed a hemorrhagic disease with a fatal outcome which we cannot identify with any recognized pathologic entity. On analysis of the factors usually involved in pathologic bleeding, a severe hypoprothrombinemia was found. The prothrombin values showed phasic fluctuation not correlated with our therapeutic efforts. There was clinical evidence of liver damage at one time, and at autopsy we found granulomas, probably of tuberculous origin. However, we were not able to recognize in the clinical and pathologic findings any of the known mechanisms of prothrombin deficiency. Hence, we have classi-

fied this condition as idiopathic hypoprothrombinemia. Because this case differs in certain essentials from the 4 previously reported cases of idiopathic hypoprothrombinemia, as indeed the reported cases differ among themselves, we are not of the opinion that these 5 cases represent a pathologic entity. Nevertheless we feel that they should be grouped together pending the development of a more adequate knowledge of the prothrombin mechanism.

Clinical Course. The patient, a white male, aged 56, was admitted to this hospital, Feb. 1, 1943, because of bleeding from the nasopharynx and into the tissues of the left leg and thigh of 2 weeks duration. The family history was negative, particularly in regard to hemorrhagic diseases. The past history was essentially negative except for unusual bleeding which attended a hemorrhoidectomy on Oct. 31, 1942, and required suturing of bleeding points on the 4th postoperative day. Further history of possible significance was the death of one of the patient's pure bred bull dogs of leptospirosis in October 1942. Shortly after admission to the hospital further ecchymoses appeared over the right anterior chest wall. The physical examination was otherwise negative except for a sallow color and marked periapical dental sepsis with some bleeding from the gums. The hemoglobin measured 37%. The patient was given a transfusion of 500 cc. of whole blood, and started on parenteral liver extract and liver and iron by mouth. His condition improved steadily until February 17, at which time there was a recurrence of bleeding from the nasopharynx and massive hemorrhages into the calves of both legs, followed immediately by hematemesis and gross hematuria. On February 23, the serum appeared definitely icteric. On February 24, he suffered a severe reaction from a transfusion of 500 cc. of whole blood, and on February 26 became deeply jaundiced. The stools were not acholic. The liver enlarged 3 fingers below the costal margin, and the spleen became just palpable. There was diffuse abdominal tenderness interpreted as indicative of retroperitoneal bleeding. However, this might have been a manifestation of the retroperitoneal growth which was discovered at autopsy.

As indicated in Figure 1, these events were accompanied by an extreme drop in the prothrombin and hemoglobin values and a sharp increase in coagulation time and icterus indices. During this crisis, treatment consisted of daily blood transfusions and intravenous glucose and saline. In addition, he was given parenteral Synkamin (4-amino-2-methyl-naphthol hydrochloride), 1 cc. every 4 hours for 10 doses, followed by 1 cc. daily. The blood factors improved, the bleeding stopped, the fever and jaundice subsided, and there was gradual improvement for 1 month.

On April 1, there was a recurrence of bleeding from the gums, vague abdominal pains, nausea and vomiting. After 2 transfusions, symptoms subsided. However, toward the end of the month there was another profound drop in the prothrombin values followed in a few days by another episode of widespread bleeding into the tissues. Blood transfusions were given almost daily thereafter until the patient died on July 19. A remission, with high prothrombin values occurred between May 8 and 18, followed by another peak of prothrombin values (this one, however, reaching only 45), another low, and a peak of 25. As the chart shows, the undulations of prothrombin values became shorter and shallower. The bleeding became virtually continuous despite therapeutic efforts which included parenteral vitamin K, oral klotogen and bile salts, intravenous calcium gluconate, and multiple vitamins.

On June 10, the patient was transferred to Belmont Hospital, Chicago (service of Dr. O. Richter). A sternal puncture was said to reveal normal marrow components. In addition to the above therapeutic measures the patient was given fibrin and fibrinogen orally, ceanothyn (a ceanothus extract), thromboplastin intramuscularly and cobra venom. In spite of these efforts, bleeding could not be controlled, and on July 11 the patient returned to the Clinic. He was emaciated and there were widespread hemorrhages into the

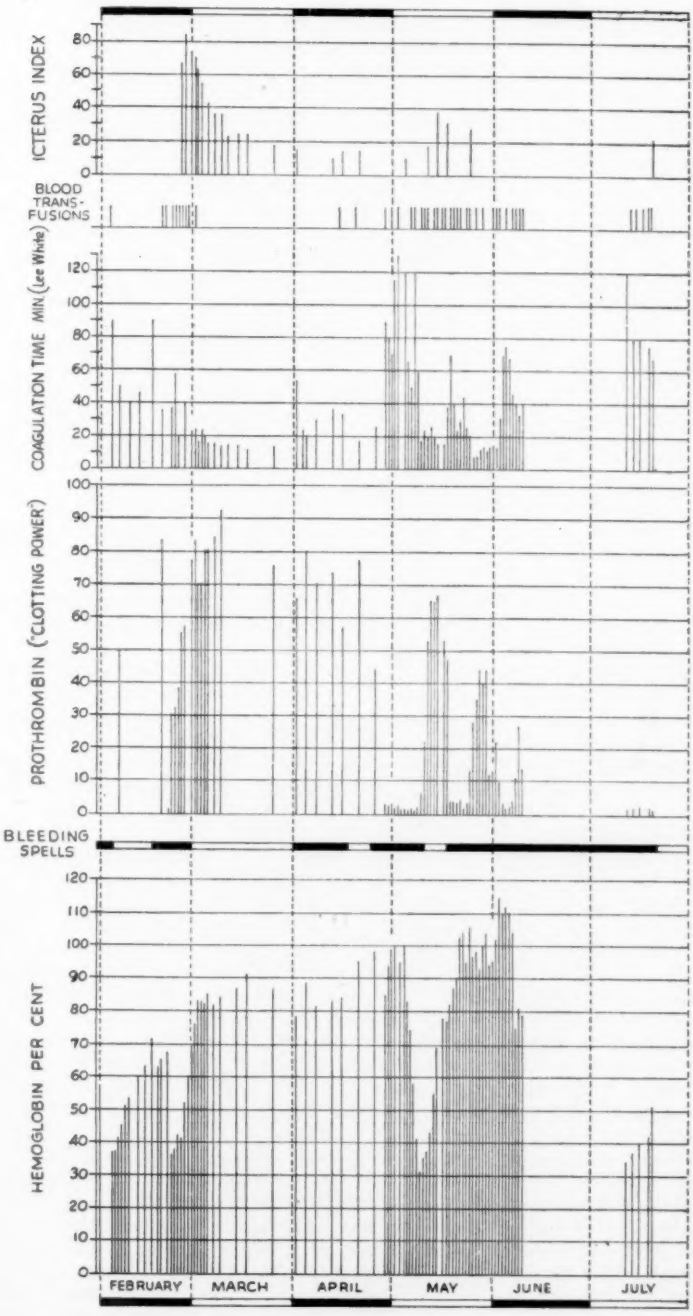
ICTERUS INDEX
BLOOD TRANSFUSIONS
COAGULATION TIME MIN. (Lee White)
PROTHROMBIN ("CLOTTING POWER")
BLEEDING SPELLS
HEMOGLOBIN PER CENT
FEBRUARY
MARCH
APRIL
MAY
JUNE
JULY

FIG. I

tissues. There had been no further abdominal pains and there had been no cough at any time. On July 18, the signs and symptoms of a cerebral hemorrhage appeared, and on the next day the patient died.

Laboratory Studies. The more significant laboratory findings and a few clinical observations are charted in Figure 1. In addition thereto, a roentgenogram of the chest was negative on February 16. The bleeding time (Duke), examined 5 times in February, ranged from 1 min. 15 sec. to 4 min. The platelets, counted 4 times in February, ranged from 198,000 to 277,000. The clot retraction observed on 4 occasions was uniformly very poor. There was no increased fragility of the erythrocytes on February 5. The tourniquet test was negative. The patient belonged to Blood Group III and was Rh-negative. There was no evidence of anti-Rh agglutinins on February 26. The erythrocyte counts roughly paralleled the hemoglobin estimations with color indices of 0.75 to 1. Repeated leukocyte counts ranged from 4850 to 11,850 with no variations in the white cells which could not be accounted for on the basis of blood loss and absorption. The erythrocyte sedimentation rates ranged from normal to 80 mm. in 45 min. An anti-prothrombin assay on February 25 was carried out in the following manner: The patient's blood was mixed with the blood of a normal control in equal parts. The prothrombin time of the control blood was 40 sec. The prothrombin time of the mixture was 60 sec. This limited prolongation was considered due to dilution and was not thought to indicate the existence of an excess of antithrombin or anti-prothrombin in the patient's blood. The seroreactions for syphilis and Weil's disease were negative. The blood calcium measured 9.4 mg. %. On February 26, the total plasma protein was 6.04, the albumin 3.04 and the globulin 2.37 gm. %. The fibrinogen was 0.63 gm. %. The blood urea measured 98 mg. % on February 27, 42 on March 1 and 20 on May 12. A bromsulphalein liver function test on February 22 showed 5% retention of dye in 30 min. and 5% in 1 hour. The Takata-Ara test was done on February 27 and March 2 and showed no precipitation in the first 3 tubes. Urobilinogen was present in the urine and feces on February 27. Urinalyses were not significant except for the episode of gross hematuria and the presence of occasional red cells and casts thereafter.

Autopsy. There was evidence of old and recent hemorrhages, widespread throughout the subcutaneous, subpericardial, subendocardial and subperitoneal tissue. There was some fresh blood in the lungs, and in the intestines. The organs showed the changes characteristic of anemia.

The lungs were heavy, their cut surface bluish pink, and the parenchyma of only the right middle lobe was normal. There was a caseous area in the right lower lobe. Three areas of the lungs were examined microscopically. The first section contained several typical tubercles with giant cells in the center, epithelioid cells around them, and a wall of lymphocytes at the periphery (Fig. 2). The second section showed fibrosis, and a few fibrotic tubercles. The third showed frank intraälveolar hemorrhage, and, again, a few miliary foci. No tubercle bacilli were found in appropriately stained slides.

The liver was slightly enlarged, and the interlobar septa more marked than normal. On microscopic examination, the liver cell columns were slightly narrowed. In several areas there were small infiltrates in the center of the acini, some of them consisting of round cells, others chiefly of fibrous tissue (Fig. 3), some were hyalinized. The appearance and distribution of these foci suggested a portal-hematogenous liver tuberculosis of some duration.

Tumor masses were found in large number around the radix mesentery and also along the abdominal aorta, throughout the mediastinum, in the hilum of the spleen, in the parenchyma of the left kidney, all along the greater curvature of the stomach, in several areas of the intestinal wall, and in the tail of the pancreas. The masses could be separated from the spine; they were hard, firm, white and did not show any gross areas of necrosis. Several portions were examined microscopically. One, from the tail of the pancreas showed cells with sparse cytoplasm and large nuclei embedded in a fibrillar stroma. The nuclei were round to oval, contain little chromatin, and several minute

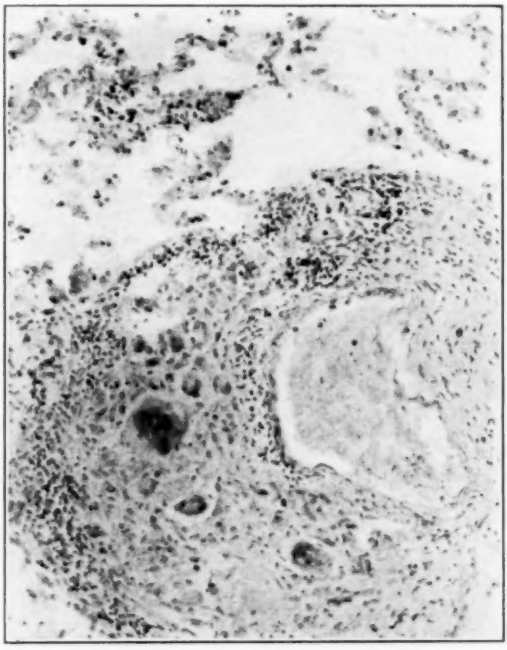

FIG. 2.—Granuloma (tuberculous) in the lung. Giant cells of Langhans type, epithelioid cells, peripheral round cell infiltration. Hem.-eos., 100×.

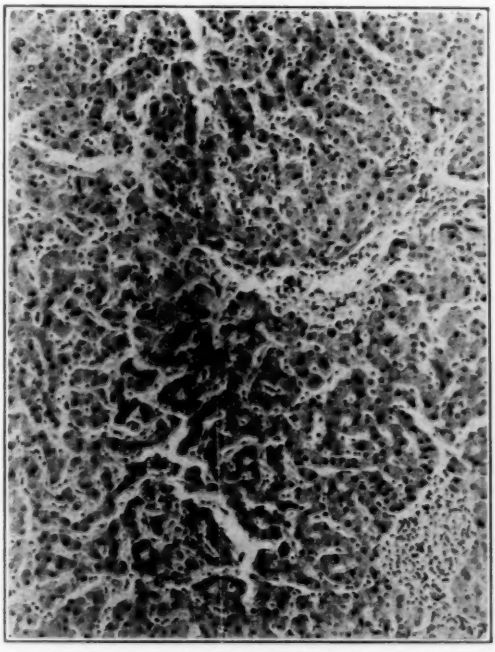

FIG. 3.—Liver. Cell columns slightly narrowed. Fibrous tissue in the lower right corner. Hem.-eos., 100×.

nucleoli. There were giant cells of the Dorothy Reed-Sternberg type: 3 to 6 large, oval, fairly dark, densly packed nuclei. A few eosinophils were lying among the other cells, and there was a fair amount of mitoses present (Fig. 4). Another portion of the tumor showed a few giant cells, but mostly cells of the endothelial type and fibroblasts. There were areas of purely fibrous tissue, some of which were hyalinized. In still another portion, there were chiefly fibroblasts (Fig. 5). A fourth one showed mainly fibroblasts, small cells, and amorphous tissue which did not give the amyloid reaction. No mitoses were seen in this area (Fig. 6). No tubercle bacilli were found on appropriately stained slides of several pieces of tissue. The head was not examined.

Pathologic Diagnosis. Hemorrhages and anemia. Granuloma (probably tuberculous) of lungs, liver, lymph nodes. Hodgkin's sarcoma. Possibly sarcoidosis.

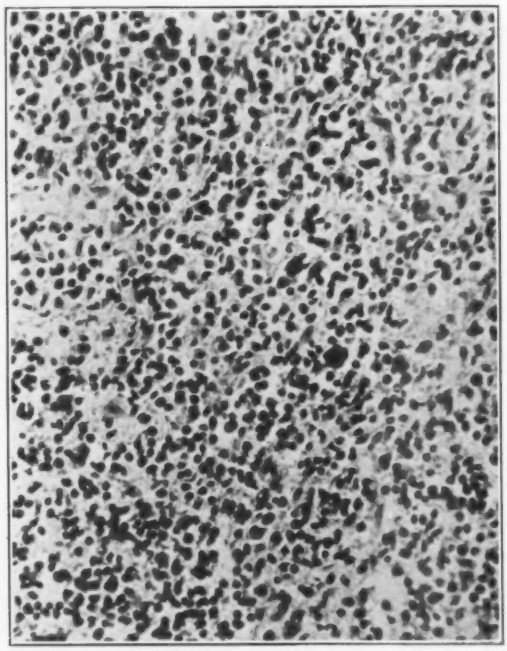

FIG. 4.—Tumor mass in the tail of the pancreas. Giant cells of Dorothy Reed-Sternberg type, and cells of epithelioid character. Hem.-eos., 230×.

The pathologic findings, however remarkable, seem inadequate to account for the clinical course of our patient. We may assume that he had a clinically latent tuberculosis of the abdominal lymph nodes, followed in February 1943 by a portal-hematogenous dissemination to the liver, and from there to the lungs. This would account for the episode of hepatic jaundice, as well as for the findings of fibrous tubercles in the liver and lungs. That there was no significant involvement of the lungs prior to this time is evidenced by the negative chest radiogram obtained on February 16. There must have been at least one more dissemination shortly before death as indicated by the presence of acute changes in the lungs. This phase was obscured clinically by the grave complications of repeated hemorrhages.

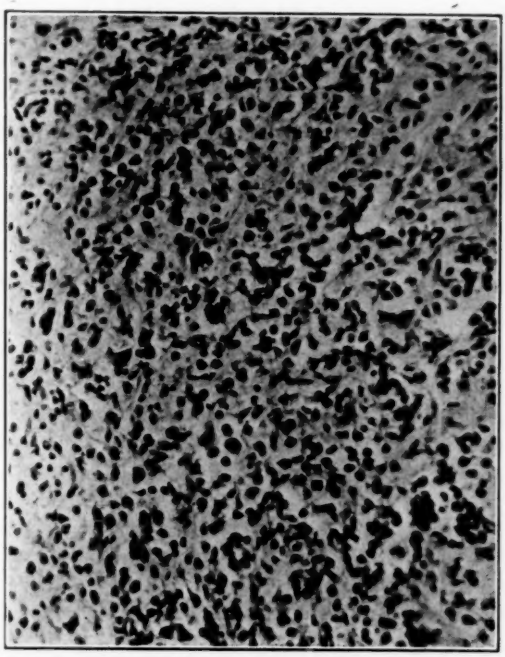

FIG. 5.—Tumorous lymph node. Sparse giant cells, epithelioid cells, and many fibroblasts. Hem.-eos., 230×.

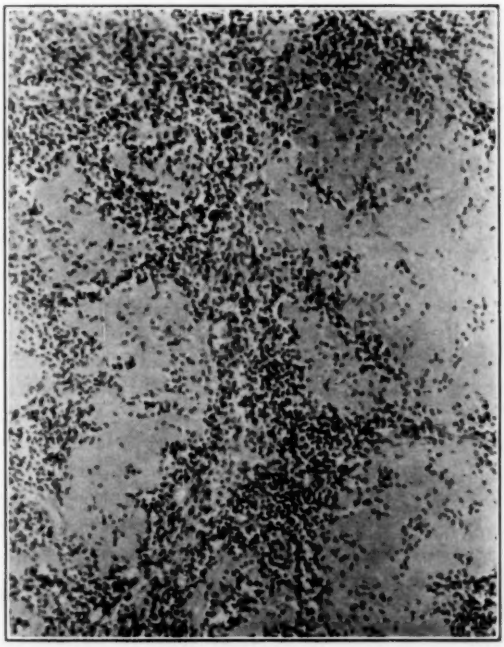

FIG. 6.—Partly hyalinized lymph node. Hem.-eos., 100×.

That tuberculosis and new-growths of sarcoma type may be related is borne out by some references to standard works. Schridde[16] describes a diffuse tuberculosis of the lymph nodes with hyperplasia of endothelioid cells. He finds this condition difficult to distinguish from sarcoma, the differentiation resting on the finding of typical tuberculosis elsewhere in the body, the occasional giant cell and on guinea pig inoculations. Bell[3] notes that "diffuse tuberculosis of the lymph nodes leads to confusion with sarcoma" and further that "difficulties are encountered in differentiating some cases of Hodgkin's disease from sarcoma, largely because the recognized types of malignant lymphomas are not sharply separable." Ewing[5] emphasizes the relationship of lymphosarcoma to Hodgkin's disease, and of both to tuberculosis. He mentions several cases wherein two or all three of these conditions were found in intimate association. He also refers to the rather frequent discovery of tubercle bacilli in lesions supposed to be purely sarcomatous. While recognizing the morphologic entities, Ewing assumes that both Hodgkin's and reticulum cell sarcoma can be caused by tubercle bacilli. The growth tendency, developed under the influence of tuberculo-toxins, can become autonomous and persist independent of the original stimulus. The case here reported belongs to the group of patients with a granuloma (probably tuberculous) associated with endothelial growth. Whether this growth should be called hyperplastic or neoplastic, we do not feel competent to decide. In either case, a causal relationship may be assumed.

We do not, however, recognize a definite connection between the hypoprothrombinemia and the other pathologic conditions. Sheely[17] claimed that the blood prothrombin tends toward lower levels in pulmonary tuberculosis. None of his 106 patients, however, had prothrombin values nearly as low as our patient. Furthermore, Gyntelberg and Dam[7] could not find any significant decrease of prothrombin in tuberculous patients with hemoptysis. Neoplastic diseases, in general, do not decrease the prothrombin values either. Some studies on blood coagulation in neoplastic diseases have been done, but they are isolated and their results controversial.[18]

Hypoprothrombinemia is known to occur in 3 well-defined situations.[4,10,12,14] First, in vitamin K deficiency, either primary or secondary due to faulty absorption from the intestinal tract. Second, in poisoning with dicoumarin and chemically related substances (salicylates[8,11]). Third, in severe liver damage. In addition, 4 cases have been described as "idiopathic hypoprothrombinemia" which do not fit into any of the 3 recognized groups.[2,6,9,15] Here we can exclude vitamin K deficiency as causative factor by the lack of any evidence of malnutrition, and by the therapeutic failure of several vitamin K preparations. We can also dismiss the possibility of drug causation because the patient did not receive salicylates or any other drugs in significant amounts for a significant period of time.

The possibility of liver damage causing the hypoprothrombinemia in our case requires a more detailed discussion. About 1 of 6 patients with hypoprothrombinemia is vitamin K-fast[1,13] and, as a rule, these

cases show severe liver damage: acute yellow atrophy, cirrhosis,[10] metastases,[12] cholangitic cirrhosis, pylephlebitis with multiple liver abscesses, gas bacillus infection of the liver,[1] and so on. Mild hepatitis is often accompanied by moderate hypoprothrombinemia which responds favorably to therapeutic measures designed to improve the liver function. In animal experiments, only very severe damage to the liver causes significant hypoprothrombinemia; *i. e.*, resection of two-thirds or all of the liver, and long-sustained chloroform anesthesia.[10,14]

There are two significant reasons why we feel our patient's hypoprothrombinemia could not have been due to liver damage. First, the amount of liver damage found at autopsy was small. Second, the timing of the hypoprothrombinemia and the manifestations of liver damage does not bespeak a causal relationship between the two processes. At autopsy, the liver showed some fibrous foci which were interpreted as residual changes of a portal-hematogenous liver tuberculosis. The liver parenchyma as a whole showed very little evidence of damage; not more, in fact, than we are accustomed to seeing in individuals who die after an illness of several months duration. This liver (Fig. 3) does not at all compare with those reproduced by Rhoads[13] where more than one-half of the liver parenchyma was definitely destroyed. It does compare, however, with the liver showing only slightly narrowed cell columns found in a case of idiopathic hypoprothrombinemia.[15]

The patient had 1, possibly 2, severe spells of pathologic bleeding before any liver damage became manifest. The liver function test on February 22, before icterus had developed, gave a negative result. The icterus subsided, but the bleeding spells, with marked delay of prothrombin time, kept recurring. After episodes of bleeding, the patient occasionally became subicteric, without again showing signs of intrahepatic jaundice. Thus, the episode of intrahepatic jaundice, in February and March, began after the bleeding tendency was fully developed, and ended without terminating the hypoprothrombinemia.

After having eliminated the three recognized causes, or groups of causes, of hypoprothrombinemia, *viz.*, vitamin K deficiency, dicoumarin poisoning, and severe liver damage, we compare our case with the 4 other published cases of hypoprothrombinemia of unknown origin. All 5 cases showed severe hypoprothrombinemia with spells of pathologic bleeding, all were vitamin K-fast, none showed any evidence of serious liver impairment, and all had normal platelets. Here, however, the consistency ceases. Important facts of the histories of the 5 cases are tabulated below, and the discrepancies are evident at a glance.

The onset of symptoms occurred in early youth in Cases 1, 2, 3 and 4; in adult age in Case 5. The course was chronic in the former cases; subacute in the latter. The family history was negative in Cases 1, 2 and 5; positive in Cases 3 and 4. The venous coagulation was normal in Cases 3 and 4; delayed in Cases 1, 2 and 5. The clot retraction was not examined in Case 1; it was normal in Case 4, slightly delayed in Case 3, sometimes normal, sometimes poor in Case 2, and always

poor in Case 5. The bleeding time was normal in Cases 1, 3 and 5; sometimes prolonged in Cases 2 and 4. The tourniquet test was not reported in Case 1; it was negative in Cases 2, 4 and 5, and positive in Case 3. Concluding, there are no 2 cases which show identical characteristics in regard to these important factors. It would seem, therefore, that these cases termed "idiopathic hypoprothrombinemia" represent more than one disease. However, we feel that attempts to differentiate should be postponed until more cases are recorded, and more is known about the nature of prothrombin, and the mechanism of its production.

TABLE 1.—CASES OF HYPOPROTHROMBINEMIA OF UNKNOWN ETIOLOGY

Case No.	Author	Age at onset	Family history	Course	Coagulation time	Clot retraction	Bleeding time	Tourniquet test
1	Beard	Infancy	Negative	Chronic	Delayed	Not reported	Normal	Not rep.
2	Rhoads and Fitz-Hugh	Infancy	Negative	Chronic	Delayed	Sometimes normal, sometimes poor	Sometimes normal, sometimes prolonged	Neg.
3	Giordano	5 years	Positive, bisexual	Chronic	Normal	Slightly delayed	Normal	Pos.
4	Murphy and Clark	4 years	Positive, bisexual	Chronic	Normal	Prompt	Frequently prolonged	Neg.
5	Authors	56 years	Negative	Subacute	Delayed	Poor	Normal	Neg.

Summary. 1. A case of hypoprothrombinemia has been presented. The disease occurred in an adult male, progressed in spells, and led to death within a few months.

2. Three recognized groups of causes of hypoprothrombinemia, *viz.*, vitamin K deficiency, dicoumarin poisoning, and severe liver damage were ruled out. Hence, the case was classified as "idiopathic hypoprothrombinemia."

3. A comparison of the case here reported with previously reported cases showed certain fundamental differences which would seem to indicate that "idiopathic hypoprothrombinemia" is not a disease entity.

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APLASTIC ANEMIA TERMINATED BY REMOVAL OF A MEDIASTINAL TUMOR

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Tumors of the anterior mediastinum may arise from a great variety of structures and their origin is sometimes obscure. Heuer and Andrus[3] have called attention to their diversity and to the fact that many are resistant to radiotherapy, but removable surgically without great difficulty With the exception of tumors of aberrant parathyroid[1] and those arising from the thymus[5] there are no known mediastinal tumors which have general effects. Tumors apparently associated with anemia, either through influencing blood formation or its destruction, have been reported. Opsahl[7] described a patient with myasthenia gravis who developed aplastic anemia and who at autopsy was found to have a thymic carcinoma; it is not certain, of course, whether this patient's anemia was directly related to the tumor. On the other hand, West-Watson and Young[9] and Singer and Dameshek[8] have each reported a single instance in which a severe anemia was relieved following extirpation of a tumor. In both instances the anemia was of the hemolytic type and the neoplasm was an ovarian teratoma.

Anemia due to hypoplasia of the bone marrow with failure of regeneration of erythrocytes, but no great leukopenia, has been described in infants by Diamond and Blackfan.[2] These children resisted all treatment and could be maintained by repeated transfusions only, but none were associated with any evidence of tumor. Similar types of anemia, also without associated tumor, have been described in adults by Mackey[6] and Kark.[4] In the adult cases, excessive storage of blood pigment in liver and other organs followed prolonged maintenance by blood transfusion and resulted in a terminal picture of hemochromatosis.

The patient whose history is presented here, had a tumor of the anterior mediastinum which appeared to be benign and of epithelial origin. She at no time exhibited any symptoms of myasthenia. Following removal of this tumor the patient's ability to build red blood cells, which had been practically absent for 18 months before operation, returned dramatically to normal. One year after operation the patient developed an apparently trivial infection, after which there appeared ascites, liver enlargement followed by jaundice and death. Autopsy revealed no evidence of the original tumor and an extensive deposit of blood pigment in many viscera suggesting hemochromatosis. This very unusual combination of events warrants publication of a single case in detail.

Case History. A 58 year old housewife was admitted to the Presbyterian Hospital for the first time on September 30, 1941, having been sent in by her own physician because of persistent anemia. In 1936 she had pneumonia, which was followed by a mild persistent cough. On October 7, 1938 she first consulted her doctor for a "bronchial cold" with increase of cough, but no fever or hemoptysis. Roentgenogram of the chest showed a large, sharply demarcated, round mass protruding from the mediastinum into the left upper lung field. Between October 29 and November 23, 1938 she was given 1600 R units of radiotherapy. Symptoms of cough subsided and remained absent for 3 months. Cough then reappeared, and between February 4 and March 31, 1939 she received 1100 R units divided equally between anterior and posterior mediastinal fields. No significant change in the size of the mediastinal mass could be demonstrated by roentgenogram.

The patient then felt well until December, 1940 when she developed weakness, fatigability and dyspnea. Her local doctor found her to be extremely anemic (hemoglobin 28%) and admitted her to St. Elizabeth's Hospital, where roentgenograms suggested that the mediastinal shadow had increased somewhat in size. Three transfusions of 500 cc. were given and she was discharged considerably relieved. She then received 8 indirect blood transfusions of 500 cc., on an average of every 3 to 4 weeks. At the same time she took liver extract, thiamin, iron, pentonucleotide and estrogenic hormones with no effect on the anemia.

Examination on admission to the Presbyterian Hospital showed an extremely pale, somewhat obese, middle-aged woman with no evidence of organic disease, other than dullness to percussion with diminished breath sounds over the left parasternal area above the area of cardiac dullness, extending 9 cm. to the left in the 3rd and 4th interspaces. There was a moderately harsh systolic murmur, presumably hemic, at the cardiac apex and transmitted to the base.

Laboratory examination: hemoglobin 1.5 gm. (10%); R.B.C. 1,000,000; W.B.C. 10,000 with neutrophils 48 (0-9-39), eosinophils 3, basophils 3, lymphocytes 38, monocytes 8%. Spread: the red cells showed slight anisocytosis but otherwise appeared normal; the white cells were normal adult forms; platelets were plentiful; no parasites were seen; mean red cell diameter 7.2. Blood platelets 204,000. Reticulocytes 0%. Bleeding time 45 seconds. Capillary clotting time 4½ minutes. Capillary resistance 30. Fragility test normal, hemolysis commencing at 40% saline. Sedimentation rate (Westegren) 60 mm. per 1 hr., but later fell to 28. Urine and stool examinations negative. Wassermann test negative. Serum protein 5.8, albumin 4.4, globulin 1.4. N.P.N. 33 mg. %. Serum cholesterol 101 mg. % with free 30 and esterified 71, but subsequently 155 with free 36 and esterified 119. Serum alkaline phosphatose 3.5 B.U. Serum inorganic phosphorus 3.9 mg. %. Blood group A. Cephalin flocculation negative. Gastric "expression" showed a free acid of 80—20 minutes after histamine injection.

Roentgenograms of the skeleton and gastro-intestinal tract, including a barium enema, showed no abnormalities. Films of the chest revealed a well circumscribed, circular shadow projecting from the mediastinum into the left lung field, at the level of the hilum. It was of the same size as in a previous film, and laminographs located it as lying in front of the bronchial tree without deforming it.

Sternal marrow biopsy showed mild hypoplasia of bone marrow, but no abnormal cells.

The patient was treated with liver extract (1 cc. of Lederle's Concentrated given intramuscularly daily for 15 days), but had no reticulocyte response. She was given 2 whole blood transfusions and 1 large red cell infusion, and was discharged on October 17, 1941 with a hemoglobin of 51%, R.B.C. 2,400,000. She then took 0.2 gm. of ferrous sulphate 4 i.d. and liver extract was continued. In spite of these measures she was readmitted on November 25, 1941 with a hemoglobin of 20%, R.B.C. 800,000. The blood Kline test on 4 occasions ranged from negative to 4+; the blood Wassermann, however, was

negative in the alcoholic antigen on every occasion. The cholesterol antigen ranged from 2 to 4+. Potassium iodide was given for 9 days as a therapeutic test without any effect upon the mediastinal mass or the persistent anemia. A total dosage of 1500 R of Roentgen ray radiation therapy was then given in 13 exposures. This produced no effect upon the mediastinal mass, which on direct comparison with plates taken 3 years previously appeared to have remained the same size over that period (Figs. 2 and 3). During this admission her blood count was built up by repeated transfusions and red-cell infusions (Fig. 1) to the level of 4,400,000 with 83% hemoglobin, at the time of discharge on January 7, 1942. On this admission surgical removal of the mediastinal tumor was first considered, but was deferred because of the patient's condition and her reluctance to accept operation. No liver or iron was given because it was felt that a sufficient therapeutic trial had proved them ineffective.

During the next 6 weeks her hemoglobin fell progressively to 26% and 5 transfusions were required to restore it to 75%. Then for 3 months she was maintained by periodic transfusions for each of which she was admitted overnight to the hospital.

She was readmitted to the hospital on June 25 for reconsideration of operation. At that time her hemoglobin was 58% and she appeared pale and weak. She also was suffering from a respiratory infection, accompanied by a moderately severe cough with a temperature of 100.4° F. and some râles at the bases of both lungs. It was felt that when her condition could be sufficiently improved, surgical removal of the mediastinal tumor should be done for 3 reasons: (1) to settle its nature and relationship, if any, to the anemia; (2) because, though stationary in size for 4 years, it might at any time increase in size, in which case it would cause pressure symptoms and be more difficult to remove; (3) any such tumor is capable of malignant degeneration. On conservative treatment her temperature returned rapidly to normal and her respiratory symptoms disappeared within the first week. After receiving 3 transfusions, she refused operation and returned to her home.

During August and September she was admitted periodically for transfusions, but on 3 occasions had reactions (chill, fever and once vomiting and a sense of choking). She began to dread receiving blood and her hemoglobin averaged only about 40% during the period. Palpitation, tachycardia, and ankle edema developed, though her venous pressure after a few hours of bed rest was 90 mm. of saline. By October she had decided to accept operation in the hope that it might help her anemia, though no real expectancy of such an effect was held out to her.

She was readmitted on October 6, 1942. During the next week she received 2500 cc. of whole blood in 3 transfusions with a resultant rise of hemoglobin from 30 to 60%, and of red cells from 1,300,000 to 4,000,000. No reticulocytes were found on 3 counts at different times.

On October 16, 1942 a spherical tumor mass was removed from the anterior mediastinum through a transpleural approach. The tumor was solid and well encapsulated, lying in close approximation to the pericardium inferiorly and posteriorly, and extending up across the pulmonary artery superiorly to the aortic arch. Laterally it was bounded by the mediastinal surface of the left upper lobe to which it was quite adherent. Medially the fatty tissue of the anterior mediastinum was also adherent to it, and from this tissue numerous blood-vessels of moderate size entered the tumor. In order to excise the tumor it was found necessary to divide the left phrenic nerve, after which the mass was shelled out without difficulty. The mediastinal pleura was closed and the chest closed without drainage after reëxpansion of the left lung. She was given a transfusion of 1000 cc. of whole blood on the operating table.

Pathologic examination of the tumor showed it to be a soft, fleshy, light-colored tumor mass of homogenous structure, measuring 8 x 6 x 5 cm. and weighing 185 gm. (see Fig. 5). Fine lobulations were apparent, but no areas of degeneration or cyst formation.

Microscopic examination showed a uniform cellular tumor consisting of 2 cell types (Fig. 6). The most prominent were moderate-sized, spindle-

shaped, well defined cells with plump oval nuclei, arranged in no definite pattern. Cells of the other type were scattered irregularly throughout the tumor; they had small, dark, dense nuclei, and in most respects appeared identical with the many lymphocytes seen in the vascular channels. No

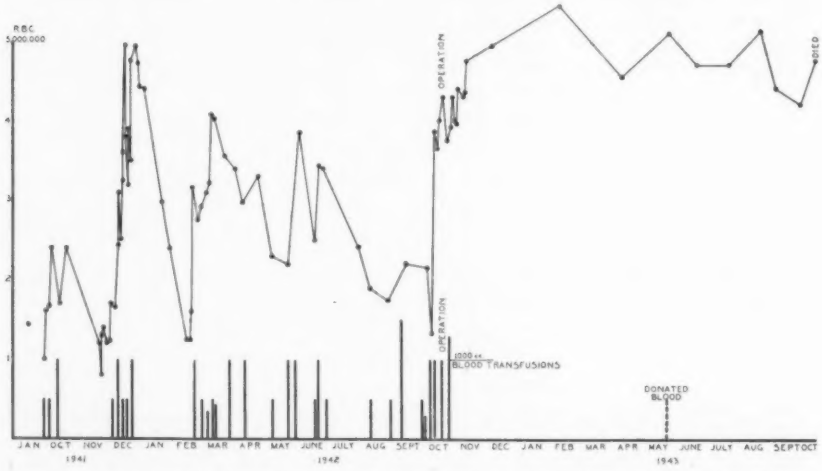


FIG. 1.—Chart of blood cell counts. Note the changes in erythrocyte count in relation to repeated transfusions and operation.

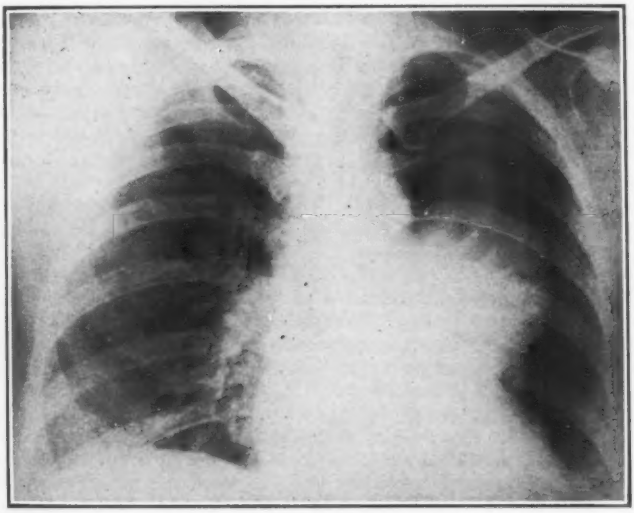


FIG. 2.—Roentgenogram of chest in 1938. There is a large circumscribed circular shadow protruding from the mediastinum into the left lung field.

mitotic figures were seen. The tumor was encapsulated by a relatively acellular and avascular tissue which was not infiltrated by the tumor cells. The origin of the tumor was not apparent. However, it was considered probable that the tumor was not malignant and further study with special stains

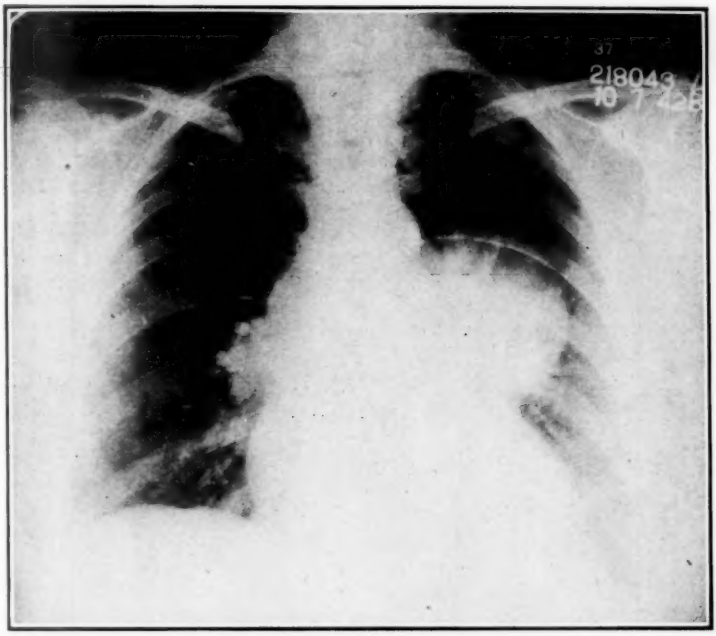


FIG. 3.—Roentgenogram of chest in 1942—a few days before operation. The mediastinal shadow shows practically no change when compared with picture taken in 1938.

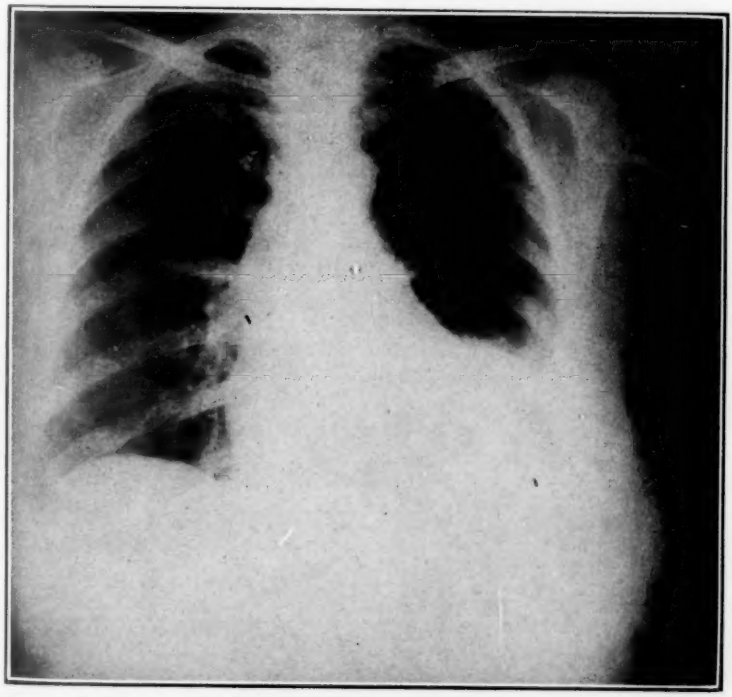
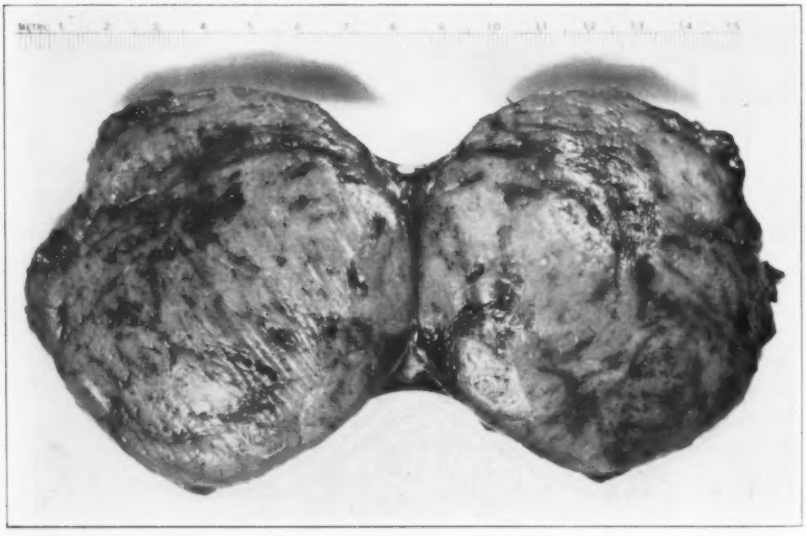


FIG. 4.—Roentgenogram of chest in 1943—10 months after operation. The left diaphragm is high due to the division of the phrenic nerve at operation. There is no evidence of recurrent tumor.

A



B

FIG. 5.—Photograph of tumor. *A*, External appearance. *B*, Tumor divided to show gross appearance of interior. There is no obvious lobulation and no degeneration.

revealed certain concentrically layered, solid bodies with flattened cells at their peripheries which suggested degenerated Hassall's corpuscles. Because of these and the uniform presence of the two cell types, one resembling a lymphocyte and the second a reticulum cell, the tumor was thought by Dr. Purdy Stout to be possibly of thymic origin. On the other hand Dr. A. M. Pappenheimer thought that a thymic origin was unlikely, because there was not the intimate mingling of lymphocytes and reticulum cells customarily found in thymic tumors, and because the argyrophil stroma was too abundant and tended to encircle individual cells. Unfortunately, the tumor tissue was fixed before it was appreciated that there was any relationship between the tumor and the anemia. For that reason no chemical or biologic studies were done.

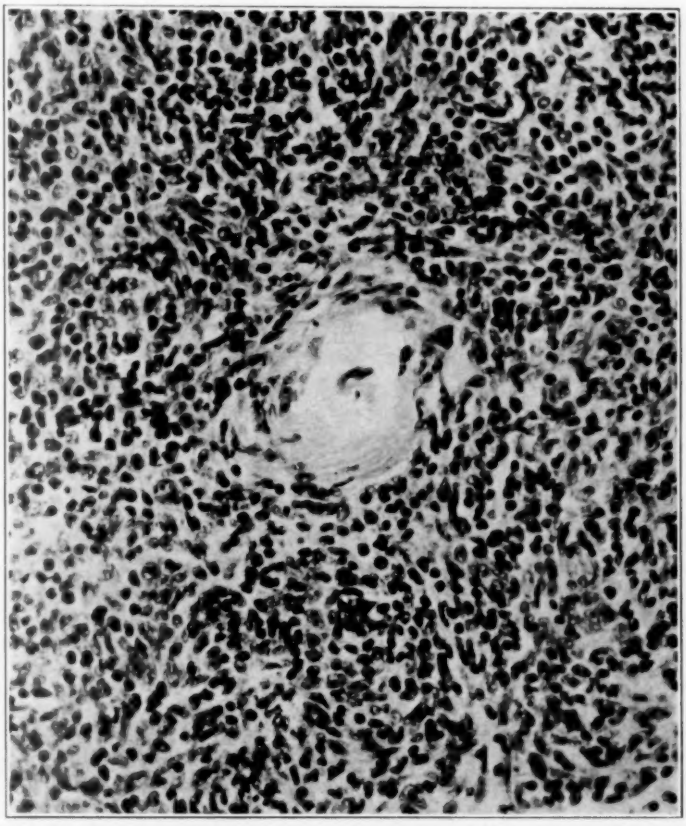


FIG. 6.—Photomicrograph of tumor, showing characteristic histology. The cells are of two types—one resembling a lymphocyte and the other a larger cell. In the center is an island of hyaline tissue, possibly representing a degenerated Hassall's corpuscle.

She reacted well to operation, though the left lung became atelectatic due to paralysis of the diaphragm and the accumulation of a moderate amount of fluid. Her temperature rose to 102° F. on the 2nd day and remained slightly elevated for 10 days, after which it returned to normal. The wound healed primarily and she was allowed up on the 8th day, walking on the 13th. On

the 3rd day after operation reticulocytes (0.8%) were found for the first time since she had been followed in this hospital. During the next week her red count decreased, but her reticulocytes increased steadily to a peak of 16.5% on the 20th day after operation. Their level then fell to 7.3% on discharge, 4 weeks after operation, at which time her red count was 4,780,000 (Fig. 7). She received no whole blood after the transfusion on the operating table, but on the 10th postoperative day was given a red cell infusion equivalent to 1300 cc. of whole blood.

During the year following discharge she received no further transfusions. Her hemoglobin varied between 90 and 108%, and her red count between 4,900,000 to 5,450,000. Her general improvement in strength and vigor was dramatic and though her left diaphragm remained markedly elevated, she had no complaints of dyspnea or weakness until September, 1943. In May, 1943 she donated 500 cc. of blood to the hospital. The next day her hemoglobin was 103%, her red count 4,700,000 and she showed a reticulocyte response of 1.5%.

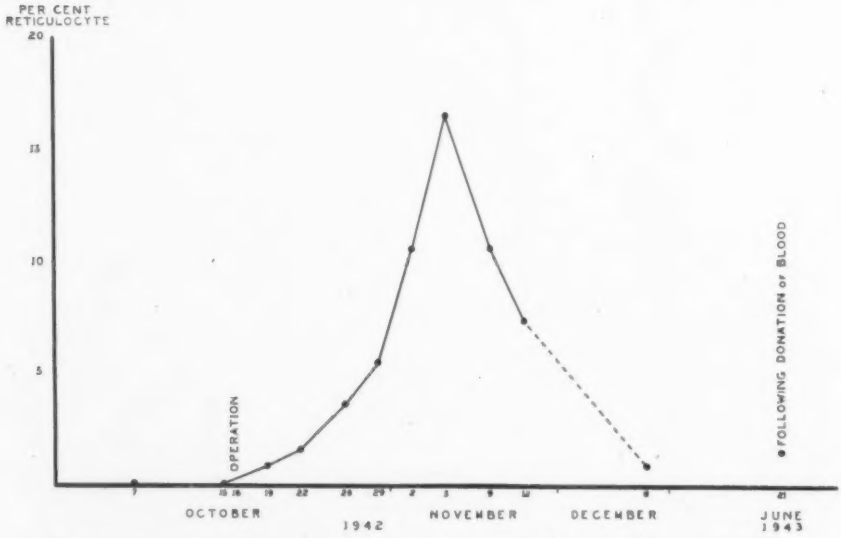


FIG. 7.—Chart of reticulocyte response. A chart to show the reticulocyte response which followed operation. During the rapid rise in the last 2 weeks of October, the erythrocyte count rose to normal, where it remained following the fall in reticulocyte count (see Fig. 1).

In August, 1943 she developed a femoral lymphadenitis, resulting from a secondarily infected epidermophytosis of the left foot, for which she was readmitted to the hospital. Physical examination at this time showed her to be well nourished and not acutely ill. The thoracic scar was well healed and examination of the lungs showed only flatness and absence of breath sounds in the left lower lobe region where Roentgen rays had demonstrated a high diaphragm (Fig. 4). The abdomen was obese, making examination difficult, but there was a sense of resistance in the right upper quadrant suggestive of an enlarged liver. No definite margin could be felt. There was a large area on the medial aspect of the left thigh, just below the inguinal ligament, which was red, indurated and tender but which showed no fluctuation. No abnormal skin pigmentation was present. The urine showed no abnormality. The red

count was 5,100,000; white count 13,100 with 72% polys. Fasting blood sugar was 120 mg. per 100 cc. Temperature, which was 102° F. on admission, fell to normal 12 days later but then rose again and fluctuated between 100° and 103° for the next 5 days during which she received sulfadiazine by mouth. The area of inflammation was then incised and a large abscess, which cultured hemolytic *Staphylococcus aureus*, was drained. Her temperature fell to normal within a few days, but the wound healed very slowly and the granulations lining it continued to look indolent for a long period in spite of careful daily dressings and irrigations with Dakin's solution. Cultures continued to show *S. aureus*, but a secondary contamination of *B. proteus* developed. Because of this wound she was kept in bed until September 10 and in the hospital until October 9. During the 2 weeks before discharge she complained frequently of abdominal discomfort and constipation and she developed a sallow appearance, although her red count remained above 4,000,000 and her hemoglobin above 95%. Examination just before discharge revealed a protruberant abdomen, which was interpreted as obesity, and some edema of the lower legs. The liver could not be felt.

She remained at home for 4 days. During this period abdominal pain rapidly increased, as well as swelling at the ankles, and a feeling of exhaustion. She was readmitted on October 13 with a fever of 101° F., which had been present for the previous 12 hours, and with acute abdominal distention. Roentgen rays of the chest showed a moderate amount of fluid in the left, and Roentgen rays of the abdomen showed gas in both large and small intestine. The following day it was obvious that she was slightly but definitely jaundiced, and that the abdomen was distended by fluid as well as by gas. Cloudy yellow fluid (2500 cc.) was withdrawn by paracentesis, following which it was evident that her liver was enlarged, being palpable 6 cm. below the costal margin and slightly tender. Although somewhat relieved by paracentesis, she became rapidly worse and on October 15 slipped into coma. Urinalysis showed no evidence of ketosis. An electrocardiogram showed nothing of significance and her hemoglobin was 110%, but circulation became progressively worse and, in spite of oxygen and digitalization, she died that evening.

AUTOPSY. The significant findings were the presence of many deposits of pigment taking the iron stain in liver, pancreas, bone marrow, thyroid, adrenals, spleen and lymph nodes. There was no pigment in the intestine or skin. The mediastinum showed a normally involuted thymus and no evidence of persistent or recurrent tumor. There was an incidental adenoma of the thyroid. Fluid was present in the abdomen and left thorax and a lobar pneumonia in the right lower lobe.

It was thought that death was related to liver insufficiency secondary to advanced hemochromatosis. Whether the chronic infection in her thigh played a part is questionable. It seems probable that the iron deposits were secondary to her repeated transfusions, since she did not show the skin pigmentation and diabetic syndrome associated with the usual hemochromatosis.

The positive Kline test, present during her year of observation and varying from 3 to 4+ is worthy of special comment. At no time was it accompanied by a positive Wassermann test in the alcoholic antigen or by any clinical evidence of syphilis. Moreover, a therapeutic trial with potassium iodide was without effect on the size of the tumor. Following extirpation of the tumor the blood Kline was still 3+ in December, 1942, but by August, 1943 it had become consistently negative. It is believed that the patient may have had

syphilis, but one can only speculate as to whether the tumor had any influence on the serologic derangement of blood proteins.

With the advantage of retrospection, it seems unfortunate that circumstances prevented earlier operation, in which case the excessive deposition of pigment following the long courses of transfusions might have been avoided.

Summary. This patient had a mediastinal tumor which had been present for a number of years, had resisted radiotherapy, but showed no signs of malignancy. During a considerable period of observation, the patient suffered from a profound depression of erythrocyte formation, although leukocytes of bone marrow origin were never deficient in number. The red cells present were not abnormal in size or shape and there was no evidence at any time of chronic blood loss or abnormal erythrocyte destruction. During this period of anemia, reticulocytes were never found on any attempt, except twice when isolated ones were seen within 48 hours of large transfusions. All of the usual therapeutic measures to stimulate red cell formation were without effect. The patient was maintained by transfusions of whole blood and saline suspensions of erythrocytes for 22 months. The mediastinal tumor was removed without difficulty, and she made an uncomplicated recovery. Following removal of the tumor, a sharp reticulocytosis occurred with a resultant restoration of the erythrocyte count to normal, where it remained for a year after operation. During this period she acted on one occasion as a donor for a transfusion, following which her reticulocytes responded normally and her blood count was not conspicuously affected. Ten months after operation she developed an abscess in the thigh which required drainage and healed slowly. Before it had healed completely, 1 year after operation, she rather suddenly developed acute ascites and jaundice, went into coma and died. Autopsy showed widespread hemochromatosis and no evidence of reappearance of the original tumor. The nature of this tumor remains in doubt, though a thymic origin was suggested.

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USE OF A SIMPLE POSTURAL TEST IN NEUROCIRCULATORY ASTHENIA

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Neurocirculatory asthenia might be defined as basically a syndrome of dyspnea, palpitation, and precordial pain during rest or upon mild exertion, noted recurringly or persistently by individuals having insufficient evidence of organic cardio-respiratory disease to account for their symptoms. At a processing center for soldiers apprehended absent without leave, we have had ample opportunity to observe the condition, often in its most acute forms. Soldiers were examined during the time that they were rigidly restricted to the post area, and in midwinter when mild respiratory infections were prevalent. At this Post, about 60% of those with potentially disabling medical disorders had neurocirculatory asthenia. Our interest in the associated circulatory phenomena arose from the need to devise an objective test for assistance in determining whether or not these soldiers were capable of performing arduous combat duty overseas, after relatively little further training.

In the past, studies concerning the etiology and abnormal physiology in neurocirculatory asthenia have yielded little that can be expressed in quantitative terms. Lewis[10] has mentioned such etiologic factors as sedentary civilian occupation, inherited weakness, the stress and strain of military life, and infections of various sorts. A large emotional factor has been suspected by many. Cobb[2] has observed, "Of course war is the most stressful phenomenon known . . ." He feels that neurocirculatory asthenia is synonymous with anxiety neurosis.

It has not been possible to link the disorder with any single organic disease. Lewis[10] differentiates it from hyperthyroidism by pointing out that soldiers with neurocirculatory asthenia have cold hands. A diminished vital capacity is not the rule.[21] Among such soldiers examined by one of us (WAJ), the basal metabolic rates and cold pressor tests (*cf.* also Wood[21]) were usually normal, whereas psychiatric consultation frequently revealed evidence of psychoneurosis. Master[12] has reviewed certain measurable tendencies which have been observed: (1) small heart and small cardiac output; (2) inadequate oxygenation of blood; (3) fainting due to inadequate venous return to the heart; (4) abnormalities in electrocardiogram after 2 step exercise.

The studies reported by Starr[19] suggest that certain patients with neurocirculatory asthenia can be shown to have abnormal cardiovascular responses to standing: what he terms "incoördination of the

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circulation." The official attitude of the Army toward this phase of the problem is indicated by the following directive:

> "*Orthostatic hypotension or tachycardia.* The blood pressure and pulse rate will be taken with the individual in the recumbent position and after standing 3 minutes. An increase in a normal pulse rate to 120 beats per minute or more when the individual stands or a decrease of a normal blood presure (when the individual is recumbent) to values less than 90 systolic and 50 diastolic when the individual stands may be considered evidence of a definite physiologic disturbance—unless the condition is very temporary following an illness, operation, or exhausted state."[20]

We have used a simple modification of a test previously employed in the study of orthostatic hypotension,[9] in an attempt to evaluate the cardiovascular responses of 1052 soldiers. We are aware of the current scepticism toward all types of tests employed to measure physical fitness,[1,4] and have, therefore, used our procedure only as an aid in separating those having transient or borderline circulatory disturbances from those who have persistent or severe abnormalities.

Indications for Test. The test to be described was performed on all soldiers in whom the initial physical examination showed one or more of the following: (1) pulse rate of 100 or more; (2) blood pressure of 150 systolic, 90 diastolic, or more; (3) blood pressure of 90 systolic, 60 diastolic, or less; (4) pulse pressure of less than 20 mm. Hg, regardless of the level of systolic and diastolic blood pressure. When time permitted, we performed the initial test after the soldier had been allowed a week to adjust to his new environment. Repeated tests were made in case of doubt, or to evaluate therapy.

Technique and Rationale of Postural Test. After the soldier had lain quietly in a comfortably warm room for about 10 minutes, the blood pressure and pulse rate were usually found to be relatively stable, as evidenced by variations of not more than 10 mm. Hg or 10 beats per minute, on two successive readings. Pulse rates were counted for 10 seconds only, in order that rapid changes in both pulse and blood pressure might be determined with ease by a single observer at intervals of 1 minute. Blood pressures were read as the nearest multiple of 5 visible on the anaeroid sphygmomanometer. The fourth phase of the Korotkoff sounds (change from clear to muffled) was recorded as the diastolic blood pressure. The subject then stood up beside his bed. Blood pressures and pulse rates were taken immediately, then after 1, 2, and 3 minutes of quiet standing. Thus, for each subject a series of six readings of pulse and blood pressure were obtained.

The oral temperature was not taken routinely, nor was it feasible to require a fixed period of fasting or abstinence from tobacco or coffee. After each test was completed, the soldier was questioned regarding his symptoms and background, and was again examined to rule out organic cardio-vascular disease.

Immediately upon standing, there are circulatory adjustments which accompany the exertion of arising, and others which act in the

same direction to oppose the hydrostatic tendency of the blood to pool inferiorly. Among those accustomed to strenuous exercise these adaptations result in small increases in systolic, diastolic, and pulse pressures and in pulse rate.[5,6,16,18] As the subject continues to stand quietly, one can usually observe fluctuating waves of change from minute to minute. We have used the *maximal* changes from the resting state observed after 1, 2, and 3 minutes of quiet standing as the basis for our interpretation.

Crampton,[3] Schneider and Truesdell,[18] and Starr[19] have reported the slight changes in pulse rate, blood pressure, and pulse pressure which usually occur upon assuming the erect position, and which have been regarded as consistent with a state of good physical training. It should be noted, however, that there were differences in the time of measuring the response to standing among the three reports mentioned above, so that exact comparison of the data of various workers is not possible. Starr[19] has concluded that it is impractical to study incoordination of the circulation upon the basis of measuring only the blood pressure and pulse rate. If one insists upon the standards for normality listed by Starr,[19] we agree that interesting trends will be missed: systolic pressure +15 to −13 mm. Hg; diastolic pressure +22 to −10 mm. Hg; pulse rate +33 to 0 beats per minute. Nor does an exact numerical index, as recommended by Crampton,[3] and by Schneider,[17] allow one to reduce the problem to one of simple arithmetic.

We have devised a classification which takes into account certain well defined clinical conditions, such as tachycardia, bradycardia, hypotension, and hypertension, and expresses the evidence of circulatory incoördination in terms of a tendency toward one or another of these clinical disorders. By so doing, we do not mean to suggest that individuals who demonstrate an abnormal trend may subsequently develop the full-blown clinical condition. On the contrary, the trend may be quite transitory, due to an acute infection, or other cause. Our observations, however, suggest that soldiers who show some of these trends are apt to complain of annoying or disabling symptoms so long as the trend toward incoördination of the circulation persists. Furthermore, our observations indicate that a trend toward the abnormal is apt to be persistent, but may vary in degree from time to time.

The possible changes in blood pressure and pulse rate which might occur with quiet standing are illustrated below: with each type of response in blood pressure, there are five possible trends in pulse rate. A total of 25 reactions, therefore, might conceivably be observed during such a test. The range of pulse rate and blood pressure which we have chosen to indicate each trend is indicated as a part of each definition.

I. Normal (Negative Test). Pulse rate between 60 and 100 while lying or standing. Blood pressure 90 to 145 systolic, and 60 to 85 diastolic, lying, and not over 145 systolic, and 105 diastolic, standing.

II. Tachycardia. (Systolic, diastolic and pulse pressures remaining normal, *cf.* I.)

A. *Persistent.* Pulse rate of over 100, on 2 or more readings while lying or standing. Variation of not more than 20 beats from lying to standing.

B. *Orthostatic.* Acceleration of more than 20 beats, *and* tachycardia of 100 or more, as *maximal* effect of quiet standing.

III. BRADYCARDIA. (Systolic, diastolic and pulse pressures remaining normal, *cf.* I.)

A. *Persistent.* Pulse rate of less than 60 on 2 or more readings while lying or standing. No decrease in pulse rate upon standing.

B. *Orthostatic.* Decrease of 20 or more beats to less than 60 as maximal effect of quiet standing.

IV. HYPOTENSION.

A. *Persistent.* Blood pressure less than 90 systolic and 60 diastolic on 2 or more readings while lying or standing. Pulse pressure greater than 10 upon standing.

1. With normal pulse rate (*cf.* I).
2. With persistent tachycardia (*cf.* II A).
3. With orthostatic tachycardia (*cf.* II B).
4. With persistent bradycardia (*cf.* III A).
5. With orthostatic bradycardia (*cf.* III B).

B. *Orthostatic.* Blood pressure less than 150 systolic, and 90 diastolic, lying. Fall in *pulse pressure* to 10 or less during quiet standing. Diastolic blood pressure not over 105.

1. With normal pulse rate (*cf.* I).
2. With persistent tachycardia (*cf.* II A).
3. With orthostatic tachycardia (*cf.* II B).
4. With persistent bradycardia (*cf.* III A).
5. With orthostatic bradycardia (*cf.* III B).

V. HYPERTENSION.

A. *Persistent.* Blood pressure of 150 systolic and 95 diastolic or more, lying, or of 150 systolic and 110 diastolic or more, standing on 2 or more readings, *save* for first pressure taken just after standing.

1. With normal pulse rate (*cf.* I).
2. With persistent tachycardia (*cf.* II A).
3. With orthostatic tachycardia (*cf.* II B).
4. With persistent bradycardia (*cf.* III A).
5. With orthostatic bradycardia (*cf.* III B).

B. *Orthostatic.* Blood pressure less than 150 systolic or 90 diastolic lying. Increase to 150 systolic or 100 diastolic upon quiet standing—*save* for first pressure taken just after standing.

1. With normal pulse rate (*cf.* I).
2. With persistent tachycardia (*cf.* II A).
3. With orthostatic tachycardia (*cf.* II B).
4. With persistent bradycardia (*cf.* III A).
5. With orthostatic bradycardia (*cf.* III B).

From the outline above it is apparent that we have selected more restricted limits for "normality" than most investigators who have employed this type of test. It should be reiterated that it was our purpose to detect soldiers who might develop disabling symptoms as foot soldiers in combat, if they were to be sent overseas after a relatively short period of further training. Many of the soldiers whom we examined already complained of such symptoms to a certain extent, and we observed that, as a group, those who exhibited a positive test had shown little aptitude, physically and emotionally, for combat duty. They might have been able to perform well in some restricted assignment, but they had not shown the aggressiveness and stamina desirable in infantrymen.

TABLE 1.—NUMERICAL INCIDENCE OF TRENDS OBSERVED IN PERFORMING 1294 POSTURAL TESTS UPON 1052 SOLDIERS WITH INITIAL ABNORMALITIES OF PULSE RATE AND BLOOD PRESSURE (those features marked with an asterisk (*) showed a statistically significant tendency to be associated as entities)

Pulse rate		Blood pressure: Normal or negative test	Hypotension: Persist.	Hypotension: Orthostat.	Hypertension: Persist.	Hypertension: Orthostat.	Total
NORMAL or Negative test:		367*	2	126	64	45	604
TACHYCARDIA	Persistent	151	4	27	68*	33	283
	Orthostatic	185	2	148*	36	32	403
BRADYCARDIA	Persistent	1	1	1	0	0	3
	Orthostatic	1	0	0	0	0	1
TOTAL:		705	9	302	168	110	1294

Results. Table 1 shows the incidence of various types of reactions, according to our classification, among the 1294 tests performed upon 1052 subjects. Statistical analysis of this information, based upon calculation of expectancies, shows the following associations to be highly significant: (1) normal blood pressure and normal pulse rate tend to be associated; (2) hypertension, especially if it is persistent, tends to be associated with persistent tachycardia (*cf.* also Fishberg, as quoted by Master[12]); (3) orthostatic hypotension is conspicuously associated with orthostatic tachycardia. Originally, we included in the test the measurement of blood pressure and pulse rate after running 40 paces, followed by compression of both carotid sinuses alternately while the subject stood quietly. After reviewing the first 260 tests so performed, these steps were discarded. No instances of carotid sinus syncope were found, even among those who had fainted repeatedly. Exercise, and the exertion of arising, seemed to exaggerate the trend of the responses observed upon quiet standing, but failed to indicate important trends not shown by the simpler test.

We are well aware that by measuring only the blood pressure and pulse rate one cannot infer with accuracy the behavior of the cardiac output,[19] the venous return to the heart, or the state of the peripheral vascular bed.[9,14] In our experience, however, this test has served as a more reliable indication of the behavior of the individual's usual circulatory responses than the taking of repeated sample readings of pulse and blood pressure, or by performing the cold pressor test on persons showing transient arterial hypertension.[8]

A group of 217 of our subjects were selected at random and retested at intervals of from 1 to 90 days after the initial test. Upon this group of men 493 tests were performed. Analysis of these tests showed a strong tendency for the identical response to be found during two or more tests: identical repetition was observed 78 times, while the chance expectancy of identical repetition was 7.5 times. In addition there was a significant tendency for orthostatic hypertension or persistent hypertension to recur in repeated tests but with variability in the pulse rate response.

The most frequent explanation for a change from a positive to a

negative test seemed to be recovery from a mild infection. Other factors noted were recovery from anxiety, fatigue, and malnutrition, and as the result of physical training for those unaccustomed to exercise. The presence of a mildly positive test is probably not incompatible with arduous physical exertion, if the soldier's will to serve is fundamentally strong, and if he can serve under good leadership.[7,13,15]

In our experience a positive test is compatible with:

(*a*) Neurocirculatory asthenia with complicating disease, such as chronic infection. (Frequent.)

(*b*) Neurocirculatory asthenia, with marked anxiety, and no demonstrable physical abnormality. (Rare.)

(*c*) Chronic infection, exhaustion, slender habitus, or poor state of physical training, without symptoms of neurocirculatory asthenia. (Rare.)

A negative test has been observed with:

(*a*) Good health and good state of physical training. (Frequent.)

(*b*) Anxiety, mild. (Frequent.)

(*c*) Mild, acute or chronic infection. (Rare.)

Summary and Conclusions. 1. Because of the need for an objective approach to the evaluation of soldiers about to be dispatched overseas for arduous combat duty, a simple postural test was devised for those showing abnormalities of pulse rate and blood pressure.

2. Standards were chosen on the basis of 1294 tests performed upon 1052 subjects.

3. A positive test can be described as a tendency toward one or another clinical abnormality of pulse or blood pressure.

4. Subjects who exhibit a positive test on one occasion are apt to do so repeatedly, unless there is a manifest change in their physical or emotional states.

5. The test appears to give a more reliable measure of the individual's usual circulatory responses than random sampling of the pulse rate and blood pressure, or application of the cold pressor test[8] to subjects showing a tendency toward hypertension.

6. It is conceded that this type of test can be influenced by emotional factors and is not a proper measure of an athlete's capacity to perform strenuous activity for short periods of time.[1] Conversely, in military medicine, this type of test can be of value in pointing out the soldier having physical disease or emotional instability and deserving of further investigation.

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SALMONELLA APPENDICITIS

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When signs and symptoms of acute appendicitis occur in conjunction with Salmonella infection, the clinical picture may become very confusing. The earlier in the course of the primary disease the acute abdominal manifestations appear, the more perplexing is the diagnosis. In a recent study of 811 Salmonella infections[7] this association was noted in 20 cases, 18 of which came to operation. In only one instance had the basic etiology been recognized prior to surgical interference. This study concerns itself with an analysis of these 20 cases.

Pain during the course of Salmonella infection is usually the result of involvement of the lymphoid tissue of the small bowel or appendix. Although in the great majority of Salmonella cases with gastrointestinal manifestations the abdominal signs and symptoms subside spontaneously, occasionally surgical intervention becomes necessary.

Study of the literature reveals several case reports of acute appendicitis in association with Salmonellosis. Widal[9] in 1913 cited the case of a 13 year old girl who developed acute intestinal manifestations, on the 6th day of a Salmonella infection. Wilde[10] in 1930 reported on a 22 year old male who was operated upon for appendicitis prior to the recognition of a preëxisting paratyphoid infection. A similar case is described by Rosenthal.[6] His patient, a 14 year old child, had severe abdominal pain for 48 hours. At operation the appendix was acutely inflamed. Enlarged Peyer's patches in the small bowel raised

the question of typhoid fever. However, a culture of the appendix revealed a Salmonella organism as the causative agent.

Muller[5] in 1933 reported the case of a 16 year old girl with gastrointestinal symptoms who, on the 3rd day of illness, was operated upon for acute appendicitis. A ruptured appendix was found. Stool cultures were positive for an organism of the Salmonella group. Hawkes[2] reported an additional case in a 23 year old male who had definite signs of acute appendicitis 24 hours after the onset of an acute generalized infection. Here, too, a perforated appendix was found at operation. Cultures of the peritoneal fluid and of the stools revealed a Salmonella organism.

Mayer[4] reviewed the foreign literature on Salmonella appendicitis in 1934. He concluded that Salmonella organisms which lodge in the appendix may occasionally, because of mechanical disturbances aroused by the infectious process, give rise to inflammatory reactions of the appendix.

Summary of Cases. In practically all the cases quoted in the literature operation revealed an appendix which had either perforated or was acutely inflamed. Of the 18 cases which came to surgery in this series histopathologic examination of the appendix failed to show an acute inflammatory process in 11. Pathologic diagnosis of these cases were as follows: normal appendix, 6; lymphoid hyperplasia of appendix, 3; and chronic appendicitis, 2 (Table 1).

The finding of enlarged mesenteric nodes at operation first called attention to the possibility of Salmonella infection in 4 of these patients. Microscopic examination of nodes which were excised in 2 cases revealed an unusual degree of lymphoid hyperplasia.

The pathologic diagnosis for the 7 other cases which came to operation was acute or subacute appendicitis, 5, and gangrenous appendicitis, 2. In spite of a preliminary diagnosis of acute appendicitis, surgery was delayed in two instances until subsidence of the acute abdominal manifestations.

All but three of the Salmonella organisms recovered from stool cultures of the 20 patients were typed* and classified according to the Kauffmann-White schema[3,8] (Table 1). The Salmonella types were as follows: *S. paratyphi B*, 6; *S. typhimurium*, 6; *S. newport*, 3; *S. oranienburg*, 1; *S. panama*, 1; and untyped, 3.

Except for the *S. paratyphi B* cases there was no apparent correlation between the Salmonella type and the pathologic diagnosis. All 6 *S. paratyphi B* cases were in the group showing no acute inflammation of the appendix. *S. typhimurium* and *S. newport* were isolated from both groups of cases.

With the exception of 5 *S. paratyphi B* infections which occurred in a single epidemic, the remainder were all sporadic cases. In the series of 811 infections previously mentioned[7] *S. typhimurium* and *S. newport* were the types most frequently recovered from sporadic

* Typing was performed by the Laboratory of the Department of Bacteriology and Serology of the Beth Israel Hospital, New York, N. Y., under the direction of Dr. Erich Seligmann.

TABLE 1.—DATA ON SALMONELLA APPENDICITIS

Patient	Age	Sex	Salmonella type	Pathologic diagnosis	Admission, white blood count (thous. per c.mm.)	Blood agglutination against *S. paratyphi B*	Duration of positive stools (weeks)	Duration of postoperative temperature (days)
E. C.	15	F	*S. paratyphi B*	Normal appendix	8.0	Negative	3	22
B. J.	20	F	*S. paratyphi B*	Normal appendix; lymphoid hyperplasia of a lymph node	5.0	Positive*	4	9
D. P.	8	M	*S. paratyphi B*	Normal appendix	5.6	Positive*	3	13
E. R.	14	M	*S. paratyphi B*	Lymphoid hyperplasia of appendix and lymph node	10.3	Positive*	5	8
M. D.	14	F	*S. paratyphi B*	Chronic appendicitis	10.6	Negative	5	12
J. P.	14	F	*S. paratyphi B*	Chronic appendicitis	7.1	Positive	3	7
R. M.	9	M	*S. typhimurium*	Acute appendicitis	17.3	Positive	3	13
B. D.	3	F	*S. typhimurium*	Normal appendix	43.0	...	1	7
B. F.	10	M	*S. typhimurium*	Lymphoid hyperplasia of appendix	11.2	...	2	7
L. C.	15	M	*S. typhimurium*	Subacute appendicitis	10.2	Positive	10	5
A. G.	8	F	*S. typhimurium*	Acute appendicitis	12.9	...	3	9
D. J.	17	M	*S. typhimurium*	Not operated upon	...	Negative	3	
L. S.	14	M	*S. newport*	Acute appendicitis	15.8	...	6	3
L. D.	9	F	*S. newport*	Normal appendix	9.2	...	4	11
I. F.	12	M	*S. newport*	Lymphoid hyperplasia of appendix	11.2	...	5	4
C. J.	42	M	*S. oranienburg*	Gangrenous appendicitis	14.0	Negative	8	10
M. K.	61	F	*S. panama*	Not operated upon	18.0	Negative	24	
L. D.	22	F	Untyped	Normal appendix	5.0	Negative	5	11
A. B.	8	F	Untyped	Acute appendicitis	...	Positive	3	8
A. J.	6	M	Untyped	Gangrenous appendicitis	16.8	Negative	9	11

* Positive in a titer of at least 1 to 40.

cases. Apparently the same general distribution as to Salmonella type holds true for the cases complicated by the signs and symptoms of acute appendicitis. There is no one type which showed a marked predilection for the appendix.

The eldest of the 18 operated patients was 42 years of age, while 16 patients were 20 years of age or younger. It has been shown that Salmonella infections, with the exception of those due to *S. typhimurium*, are fairly evenly distributed throughout all age groups.[7] It is apparent, both from this series and from cases previously reported in the literature that Salmonellosis complicated by appendicitis tends to occur primarily in the first two decades of life.

The duration of positive stools in the entire group of cases varied from 1 to 24 weeks; 11 patients were infectious for at least 4 weeks. All but 3 of the cases were released from the hospital while still harboring the causative organism.

The agglutination reaction utilizing *S. paratyphi B* as an antigen was performed in 14 of the cases. Positive tests in a titer of at least 1 to 40 were obtained in 7. In our experience, stool cultures are of far greater value than the agglutination reaction in the laboratory diagnosis of Salmonella infection.

Of the 18 cases that came to operation, at least one white blood count and a histopathologic examination of the excised appendix was available for 17. As might be expected, the white blood counts of the cases which showed no acute inflammatory changes in the appendix were, in general, lower than those in which the inflammatory process was marked. The lowest admission white count in the latter group was 10,200, while there were 6 cases in the former group with white counts of 10,000 or less. A 3 year old girl with an admission white blood count of 43,000 for which there was no explanation had a normal appendix at operation.

Case Reports. Case 1. E. R., a 14 year old boy, was admitted to the hospital on April 19, 1937 with complaints of nausea and right lower quadrant pain of 4 days' duration. The temperature on admission was 101° F., pulse 110, and respirations 20. Physical examination revealed tenderness in the right lower quadrant where there was moderate spasm. The white blood count was 10,300 with 70% neutrophils. Urinalysis was normal.

Appendectomy was performed 1 hour after admission. A grossly normal appendix was removed. An enlarged mesenteric node was excised for pathologic examination. Postoperatively the temperature remained elevated for 8 days. The white blood count dropped to 7250 on April 24, 1937 (67% neutrophils) and to 6900 on April 26 (54% neutrophils). The blood agglutination reaction was reported positive for paratyphoid B on April 26. Stool culture on May 2, 1937 was positive for *S. paratyphi B*.

Pathologic Report. Lymphoid hyperplasia of appendix and lymph node.

Case 2. L. D., a 9 year old white girl, entered the hospital on October 21, 1942 complaining of abdominal pain, nausea, and vomiting of 24 hours' duration. The pain which had come on suddenly in the mid-epigastrium localized after 24 hours in the right lower quadrant. The temperature was 100.5° F., pulse 102, and respirations 24. Physical examination was negative except for localized tenderness and spasm over McBurney's point. Rectal examination revealed some tenderness on the right side. The white blood count on October 21, 1942 was 9200 (68% neutrophils); urinalysis was negative.

Appendectomy which was performed shortly after admission revealed a normal appendix. There were several enlarged nodes in the mesentery of the terminal ileum. The temperature following operation varied from 101° to 102° F. for 48 hours and remained elevated for a total of 19 days thereafter. The white blood counts from October 21 to October 30 varied from 6200 to 5600. Stool cultures on October 29, November 6 and November 13 were positive for *S. newport*.

Pathologic Report. Normal appendix.

CASE 3. L. S., a 14 year old white boy, was admitted to the hospital on October 13, 1942 with complaints of feverishness, chills, and vomiting of 24 hours' duration. Temperature on admission was 100.6° F., pulse 112, and respirations 20. Physical examination was essentially normal. Roentgen ray of the chest on October 14 revealed normal lung fields. Urinalysis was negative.

On the 2nd hospital day there was onset of bloody diarrhea, together with generalized abdominal tenderness. Next day the tenderness became localized in the right lower quadrant. The white blood count at this time was 15,800 with 82% neutrophils. With a preoperative diagnosis of acute appendicitis, laparotomy was performed. The appendix was large, acutely injected and edematous. Postoperatively the temperature rose to 104.6° F. and remained elevated for 3 days. Stool cultures on October 14, October 19, October 28, November 3, November 9, and November 17 were positive for S. newport.

Pathologic Report. Gross: serosa injected and covered with fibrin; wall edematous and injected; lumen filled with purulent material. Microscopic: mucosa extensively eroded; wall edematous and infiltrated with a large number of neutrophils and showed scattered areas of hemorrhage; vessels engorged.

Diagnosis. Acute appendicitis.

CASE 4. C. J., a 42 year old white male, entered the hospital on February 14, 1938 complaining of nausea, vomiting, and severe right lower quadrant pain of several hours' duration. There was a past history of occasional attacks of lower abdominal pain. Temperature on admission was 99° F., pulse 82, and respirations 22. Physical examination revealed marked tenderness and spasm in the right lower quadrant, most marked over McBurney's point. The white blood count was 14,000; urinalysis was negative.

Operation, which was performed 3 hours after admission, revealed a gangrenous appendix. Subsequently temperature rose to 102° F. and remained elevated for 3 days. There was a moderate amount of purulent drainage from the operative wound. The temperature then remained normal until February 17 when it rose to 102° F. and remained elevated for 7 days thereafter. On February 25 patient had frequent watery stools. Stool cultures on March 21, March 26, and April 6 were positive for *S. oranienburg*.

Pathologic Report. Gross: markedly enlarged and thickened appendix. Microscopic: partial to complete destruction of the lining mucosa. Inflammatory reaction extends through the wall with destruction of the submucosa and muscularis.

Diagnosis. Acute gangrenous appendicitis.

Comment. Contrary to the data presented in the literature, in the majority of this series of cases the clinical diagnosis of acute appendicitis was confirmed neither at operation nor by histopathologic examination of the appendix. It must be assumed that lymphoid hyperplasia of the small intestine, appendix, or mesenteric nodes was responsible for the acute abdominal manifestations of these patients. Unfortunately, careful review of the preoperative clinical findings offered no clue which might be helpful in preventing surgical interference. In both Case 1 and Case 2 which are presented as typical of this group, involvement of the lymphoid tissue of the appendix and mesenteric nodes was the most significant pathologic finding.

On the other hand, it must be borne in mind that in some cases the process in the appendix may become very acute. In 7 of our cases the pathologic report was either acute, subacute, or gangrenous appendicitis. Although no perforations occurred in this series, 2 such cases[2,5] have been reported in the literature. Apparently organisms of the Salmonella group may produce two strikingly dissimilar pathologic entities in the appendix. Their ability to cause septic lesions elsewhere in the body has been noted previously.[1]

In Case 3, although Salmonella infection was suspected prior to the appearance of the signs and symptoms of acute appendicitis, surgery was considered essential. The findings at operation confirmed the diagnosis of acute appendicitis. Obviously, when the symptomatology is suggestive of acute appendicitis, surgery is indicated whether or not a previous diagnosis of Salmonella infection has been established.

The period of apyrexia noted only during the course of Case 4 is difficult to explain and merits further comment. Postoperatively the temperature remained elevated for 3 days. Then, after a normal temperature for 2 days, there was a subsequent rise which lasted for 1 week. It is a matter of conjecture whether this patient, subsequent to an operation for acute gangrenous appendicitis, developed a Salmonella infection unrelated to the surgical condition. On the other hand, it might be postulated that mechanical disturbance of the intestinal tract set up during the incubation period of a Salmonella infection initiated the appendiceal process.

Common to the entire group of cases which came to surgery was the persistence of pyrexia following operation. The duration of fever among the cases varied from 3 to 22 days (Table 1). Apparently an otherwise unexplained persistent postappendectomy fever should raise the question of a missed Salmonella infection.

Failure to establish an etiologic diagnosis in cases of Salmonella appendicitis may be directly responsible for the spread of infection to contacts. Epidemiologic investigation of hospitalized Salmonella cases has, at times, revealed secondary cases among hospital personnel.[7] Family contacts may become infected when patients with positive stool cultures are released from the hospital.

Recent studies suggest that a significant reservoir of Salmonella infection exists among the population.[7] Utilizing modern cultural methods, study of appendicitis cases by routine bacteriologic examination of the feces and appendix may be of considerable value in determining how often organisms of the Salmonella group are the causative agents. Salmonella appendicitis may be more prevalent than is commonly supposed.

Summary. 1. When the signs and symptoms of acute appendicitis occur in conjunction with Salmonella infection, a difficult problem in diagnosis is presented. This association was noted in 20 cases, 18 of which came to operation.

2. While histopathologic examinations of 11 of these cases failed to show acute inflammation of the appendix, in 7 instances the report was acute, subacute or gangrenous appendicitis. Review of the pre-

operative clinical findings presented no method of differentiating one group from the other.

3. Of the 20 cases, the 17 which were typed were distributed among five different Salmonella varieties.

4. *S. typhimurium* and *S. newport* were isolated from cases which showed acute inflammation of appendix and from those which did not. All 6 *S. paratyphi B* cases fell into the category in which involvement of the lymphoid tissue of the appendix or mesenteric nodes was the most significant pathologic finding.

5. Although Salmonella infections appear among all age groups, our cases of Salmonellosis associated with appendicitis occurred primarily in children and young adults.

6. Unexplained persistent postappendectomy fever should raise the question of an underlying Salmonella infection.

7. Recognition of the basic etiology in cases of Salmonella appendicitis will aid in the prevention of secondary infections among contacts in the hospital and at home.

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UNDER THE CHARGE OF
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BIOLOGIC FALSE POSITIVE REACTIONS TO THE TESTS FOR SYPHILIS

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PART II*

Lymphogranuloma Venereum. In 1922 Ravaut[245] called attention to the possibility of encountering in patients with lymphogranuloma venereum a transient positive serologic reaction for syphilis which quickly becomes negative without the intervention of antisyphilitic treatment. Later (1924), Ravaut, Boulin and Rabeau[246] showed a fleeting positive reaction in 3 of their patients and in 1 of those who, coincident with a fever, had at another time a weakly positive which disappeared definitely without treatment for syphilis. In 1925, May[199] of Uruguay met in a patient with lymphogranuloma venereum a partial positive Wassermann reaction; in 1933 he reported a similar case. He stated in 1940 that a patient with this disease observed by Professor Lamas also had a transient positive reaction. Other cases have been reported by various authors. Freudenthal[92] saw 2 cases among 51 with a weakly positive reaction (Kahn and Citichol), but the Meinicke reaction was negative. Gay Prieto[95] found 1 of 102 cases which gave negative reactions to the Wassermann and Kahn tests, but weakly positive to the Sachs-Georgi and Meinicke tests. On the other hand, other authors like Hellerström[125] (46 cases), Ruge[257] (165 cases), Buske[37] (72 cases) did not find a positive serologic reaction for syphilis among their patients.

De Gregorio[62] found 10 positive reactors among 32 patients, whereas Uribe of Colombia said that 30% of his cases gave positive reactions. Sulzberger and Wise[295] found cases in which the Wassermann reaction was positive for several weeks in the presence of an active lymphogranuloma venereum lesion, and in the absence of syphilitic infection. Frei[91b] also found many cases giving transitory false positive Wassermann reac-

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tions. Recently, Myerson[219] stated that the Kahn test may be positive early in the course of lymphogranuloma venereum, later becoming negative. Cariola[42] found 27 of 122 cases of lymphogranuloma venereum who showed positive Kahn and Wassermann tests without any signs of syphilis, 24 of whom lost the positive reactivity within 3 months. Knott and his co-workers[163] stated that such false positive reactions occurred in 10 of 31 cases of lymphogranuloma venereum, 10 of 44 cases of chancroid and 2 of 18 cases with heterogeneous genital lesions. Chana[45] of Chile reported that 20% of his 122 cases of lymphogranuloma venereum had positive reactions. He believed that the Kahn verification test was of value since he found a close correlation between the results of this test and the ultimate serologic outcome.

Alteration in the blood proteins has been noted in lymphogranuloma venereum and has been regarded as of diagnostic significance by Jersild,[141] and by Howard, Eisenman and Strauss.[133] After summarizing the observations of a number of investigators and their own work, Rosen, Rosenfeld, Bloom and Krasnow[254] support the diagnostic importance of the lipid-globulin relationship by observations on 116 cases. Hyperglobulinemia occurred in 100% of their cases, and was most marked in the late stage (rectal stricture and esthiomene). They rate this hyperglobulinemia then as a valuable diagnostic lead. The serum lipids were uniformly decreased. In chancroid, for example, there may be an increased globulin content, but there is no decrease in the lipids. These observers found that treatment of the lymphogranuloma venereum brought the lipid values to normal but left the globulin unchanged. Gutman and Wise[112] reporting on the positive formol-gel reaction associated with hyperglobulinemia may be responsible for other somewhat erratic or abnormal findings in the blood of patients with this disease. For example, the high sedimentation rate, often greatly in excess of the level consistent with the degree of obviously active infection; the falsely positive and repeatedly anticomplementary Wassermann reactions reported in the literature may be regarded as phenomena attendant upon the hyperglobulinemia.

Because of a possible relation of the Wassermann and Kahn tests to the globulin fraction of the serum proteins and because Gutman and Williams[111,321] found the Wassermann reaction to be anticomplementary in 22% of 74 Frei positive cases, the results in the Kampmeier, Smith and Larsen[151] cases are of interest. Of the 43 Vanderbilt University Hospital cases, none was found to have anticomplementary Wassermann reactions. Both Wassermann and Kahn tests were negative in 13 cases, and both positive in 9 cases. The Kahn test alone gave negative reactions in 16 additional cases. Both tests yielded a doubtful reaction in 1 case, the Wassermann was negative and the Kahn doubtful in 2 cases, and the Wassermann negative and Kahn positive in 2 cases. In the Nashville General Hospital group of 24 cases, the Wassermann test was negative in 19 instances, positive in 4, and not done in 1. Recently Kampmeier[150] reviewed the cases of rectal stricture treated in the Vanderbilt University Hospital since 1926. Most of these cases were not proven by the Frei test, but analysis of the history and physical findings made it seem reasonable that a certain percentage of them was due to lymphogranuloma venereum. In those selected as probably being cases of this disease, the Wassermann reaction was negative in 29 and positive in 16, 2 were Wassermann and Kahn positive, 6 were Wassermann negative and Kahn positive, 1 was Wassermann doubtful and Kahn positive.

Kampmeier and his co-workers'[151] findings do not agree with those of

Gutman and Williams[111] as regards the frequency of anticomplementary Wassermann reactions in lymphogranuloma venereum. (Since this study was completed, they reported an anticomplementary Wassermann and positive Kahn test were found in a patient with bubo and hyperglobulinemia.)

Because of the prevalence of lymphogranuloma venereum in the Negro population in Georgia, Beeson and Miller[16] made a study of the incidence of hyperglobulinemia in 2375 sera, from both the white and the Negro population. The formol-gel test was used to detect the presence of increased globulin. Hyperglobulinemia was found in 0.4% of white males and in 0.6% of white females. In Negroes the respective rates were 5.6 and 8.3%. The difference in prevalence of lymphogranuloma venereum infection is presumed to be the explanation of this racial difference. A higher proportion of cases of hyperglobulinemia found among Negroes with syphilis appeared to be related to the associated presence of lymphogranuloma venereum in those persons.

Jones and Rome[143] studied 79 patients with lymphogranuloma venereum, the majority of whom had total protein values above 8. The mean total protein value was 8.55 and the highest value obtained was 13.33 gm. per 100 cc. Schamberg[265] studied the course of the plasma protein changes in 20 Negroes with early lymphogranuloma venereum treated with sulfanilamide. All of these patients presented, initially, hyperglobulinemia, the globulin reacting toward the normal level as clinical improvement was manifest. Seventeen of the 20 patients in his series had total protein values above 8 gm. at one time or another during the course of their disease. Kampmeier, Smith and Larsen[151] found hyperproteinemia in 62 of the 67 cases of venereal lymphogranuloma which they studied and considered this fact to be of diagnostic value. Kagan[145] found hyperproteinemia in 8 of his 11 cases of lymphogranuloma venereum. The highest total protein in Cardon and Atlas's[40b] series of 6 cases of this disease was 11.44 gm. per 100 cc., and the highest globulin value was 7.66 gm. In their earlier paper, Cardon and Atlas[40a] commented on the fact that lymphogranuloma venereum was a disease in which biologic false positive serologic reactions and anticomplementary reactions were especially associated with hyperproteinemia. It is interesting that Taussig and Somogyi[299] found that the hyperglobulinemia which is present in most cases of venereal lymphogranuloma occurs also to a marked degree and with high euglobulin values in granuloma inguinale.

May believes[199c] that the positive serologic reactions for syphilis encountered in cases of lymphogranuloma venereum are not false but represent abortive or weak attacks of syphilis due to insufficient quantity of organisms in the inoculum, so that the body defenses are able to keep the syphilitic infection mild. This seems to us to be highly speculative.

Lupus Erythematosus. This subject is carefully reviewed by Ambrosetti.[2] Some false positive reactions have been obtained with the various serologic tests for syphilis but the majority of the patients with various phases of this complex have given negative results. Schaumann and Heden,[266] for example, found only 2 definitely positive Wassermanns and another weakly positive reaction among 75 cases. Boas and With[25] found no positive reactions among 146 patients. No positive reactions were encountered in 6 cases by Dudumi and Saratzeano[67] and in 9 by Schönfeld.[267] Gougerot and Burnier[98] noted only 1 positive reactor among 50 patients. Throne's[303] cases, 36 in number, all gave negative reactions except 1 with an antecedent history of venereal disease. Freund[93] col-

lected 23 positive reactions (9%) in a group of 249 patients. Prochazka[242] had 73 patients, of whom 49.3% had an increased anticomplementary capacity. This was present in 8.3% of 6 acute cases. The author believed the cause of this phenomenon resided in the lymphatics. Margarot, Rimbaud and Ravoire[197] observed 24% positive. Kogoj[164] had 8 positive reactors among 132 patients. Carrera[43] found 30% positive serologic reactions, while Pessano[238] noted 8.3% positive results in his 84 lupus erythematosus patients. Ambrosetti's[2] series of 108 patients studied with the Wassermann and Kahn standard tests yielded 4 positive (3.7%), 96 negative (88.8%), 2 doubtful, 1 anticomplementary. In 3 cases the Wassermann was positive but then became negative. Another case with Wassermann negative, Kahn standard negative, gave a Kahn presumptive positive reaction. In another instance the Wassermann was negative but the Kahn standard was doubtful (*i. e.*, $--+$). Ambrosetti[2] agrees with Pautrier[237] that some patients may simultaneously present lupus erythematosus and either acquired or congenital syphilis.

In this country little attention has been paid to the occurrence of positive serologic reactions to the tests for syphilis or little significance has been laid on their positive outcome. However, recently Sompayrac and Hailey[280] reported such a case with false positive Kahn reaction. In addition Coburn and Moore[49] noted that during life patients suffering from disseminated lupus erythematosus have constantly presented hyperglobulinemia involving gamma globulin. It is believed by some that it is the reaction of this gamma globulin fraction with certain phospholipids which gives rise to false positive Kline and Wassermann reactions.

Our own experience with carefully studied cases of acute and chronic lupus erythematosus would lead us to the conviction that false positive serologic reactions must be indeed rare in these states and when a positive reaction is encountered it probably represents an undiagnosed syphilis or technical error.

Tuberculosis and Sarcoid. There is great question whether tuberculosis can cause biologic false positive reactions to the tests for syphilis. This doubtful ability of tuberculosis to cause false positive reactions is confirmed by the literature and the relative infrequency of positive serologic reactions for syphilis among tuberculous groups. Nonetheless, there is a gradually expanding literature on this subject, indicating that some patients with tuberculosis yield positive reactions to the tests for syphilis without their having or having had syphilis.

In 1922, Dulaney[69] found 8 positive Wassermann reactions among 100 tuberculous patients, but did not express himself on the question as to whether or not they actually had syphilis. Kilduffe and Hersohn[158] failed to detect any positive Kolmer or Kline reactions in a group of 200 tuberculous subjects. Stuckey and Huntley[293] felt that the Kahn reaction was not affected by the presence of tuberculosis. Bowman[28] as well as Horowitz[131] also found no influence of tuberculosis, on the reactions to the serologic tests for syphilis. Snow and Cooper[278] likewise could elicit no false reactions using non-cholesterinized antigens, but they found 31% of cases giving + to 2+ reactions with cholesterinized antigen. In the first United States serologic evaluation study,[55] the percentages of positive reactions obtained in 53 cases of tuberculosis were Hinton 5.7, Kolmer 2, Kahn, Kline and Eagle flocculation tests 1.9 each. Parran and Emerson[233] reporting for a committee to study this problem reviewed the earlier literature cited above, mostly denying any significant influence

of tuberculosis on the serologic reactions. Eight out of 458 serums of presumably non-syphilitic individuals from 9 sanatoria gave positive reactions to many tests. Four of these were found to be probably syphilitic, 3 were not available for reëxamination and in 1 no evidence of syphilis could be found. These were considered syphilitics, although there is some doubt as to the justification for it. In the remaining 450 serums, 1 positive result was obtained with the Eagle microflocculation test, 4 positives with the Hinton, 1 positive with the Kahn presumptive and 5 positives with the Kline exclusion test. The Kolmer and Kahn standard tests gave negative results. Those tests giving positive results also gave a number of doubtful results. Some positive and doubtful reactions became negative on repetition. Parran and Emerson[233] concluded that "tuberculous toxemia may contribute a confusing factor to syphilis serology. It should not, however, present a major problem in the clinical interpretation of results obtained with carefully conducted serodiagnostic procedures."

Stokes[289b] thought that latent tuberculosis was responsible for false positive serologic reactions. Eagle[71c] reported a case which he concluded was probably technical rather than biologically false. Dunner and Mayer[70] in 1933 found 43 positive reactions to one or all tests used among 1200 patients with pulmonary tuberculosis. These patients also had clinical evidence of syphilis. There were 31 who gave positive reactions to one or several tests and in these there was no history or clinical evidence of syphilis; 12 of these came to autopsy without revealing evidence of syphilis; 5 of the syphilitic patients who came to autopsy likewise had no evidence of syphilis. These authors concluded that positive reactions for syphilis do occur in persons with pulmonary tuberculosis who have neither history nor clinical or autopsy evidence of syphilis. They also observed patients in whom, with the advance of the tuberculosis, negative serologic reactions to the serologic tests for syphilis became positive. The studies of S. Berg,[19] of Warring,[313] and of Sweany[296] indicate that tuberculosis probably causes only an insignificant number of false reactions. Sellek Azzi and Frade,[270] among more than 100 patients with infantile tuberculosis, obtained about 5% false positive serologic reactions for syphilis. The 1941 Washington Serology Conference[243c] showed that among about 59 patients various tests gave 0 to 6.8% non-specificity in tuberculosis of any type. The more widely used tests gave 100% specificity in any type of tuberculosis.

Although sarcoidosis is not generally accepted as of tuberculous origin, discussion of this disease is made here for convenience. The fact that Frazier and Hu[90] were able to isolate *Treponema pallidum* from a subcutaneous sarcoid need not indicate that syphilis is the cause of any type of sarcoid associated with positive serologic reactions. In 1921 Vasek[306] and in 1923 F. Berg[18] reported examples of false reactions in sarcoidosis. Waldenström[309] reported 5 patients with sarcoid with positive serologic reactions, 1 of whom had no clinical, anamnestic or familial evidence of syphilis, but did have increased sedimentation rate and hyperglobulinemia. Waldenström[309] thought this explained the serologic outcome. Reisner[250] found negative reactions in 23 of his 35 cases of sarcoidosis. They were positive in 10 and doubtful in 2 instances. All the positive or doubtful reactions occurred among the 30 Negro patients of this series. He believed that no etiologic significance could be attached to this finding, since prevalence rates[308] show 25 to 30% positive serologic reactions for syphilis among large groups of Negro patients. Antisyphilitic therapy did not

influence the clinical manifestation or course of the disease. Some of the positive cases persisted in spite of intensive and prolonged antisyphilitic therapy. Sometimes the reactions fluctuated between positive and negative.

Acute Exanthemata. Acute exanthemata have not played an important rôle in the question of biologic false reactions, largely because usually the serologic tests for syphilis are not made on such patients as a routine, and also because in all probability improved serologic techniques have indicated that such diseases as scarlet fever and measles do not often yield false reactions. In fact, Lund[191] by his method of titration of traces of reagin was unable to demonstrate more than the average level of reagin in the blood of patients with scarlet fever.

Scarlet fever has been reported the cause of some false reactions.[206] Landau[178] reported on the Wassermann, Kahn and Sachs-Georgi reactions in the blood obtained from 164 patients, mostly children, with scarlet fever. The Wassermann and flocculation reactions were positive in 1 patient. In 2 patients, the Kahn reaction alone was positive. It became negative in one in the 2nd week, and was still positive in the other in the 3rd week. When the tests were repeated in 2, 3 and 4 weeks, only the Sachs-Georgi reaction was positive in one patient during the 2nd week, but was negative thereafter. The author concluded that scarlet fever is not the cause of non-specific serologic reactions. Monticelli,[209] on the basis of negative results with 364 Wassermann tests (Frankfurt method) on the serums of 150 children with scarlet fever, concluded positive serologic reactions reported in scarlet fever are due to varying sensitivity of the antigens used. He advises standardization of serologic procedure for serologic tests for the various countries.

In 1932 Gunn[110] found occasional false positive reactions in patients with measles and chickenpox. He stated that in acute fevers there is an increase in the normal lipoidophil antibody content of human serum or a transient physical or chemical alteration of its composition which permits complement fixation to occur even in the absence of syphilitic infection. These may be present from the 3rd to the 21st day and rarely persist into the 4th week. His 6 serums from patients convalescing from mumps gave negative reactions. W. Smith[277] found 2 siblings with positive sigma reactions 6 weeks after the onset of mumps. Their parents were negative, and 1 of the patients died of mumps encephalitis. He had a weakly positive Wassermann in blood and cerebrospinal fluid.

In measles, Pockels[240] reported several positive reactions among 206 children studied 1 to 2 weeks after the onset of the disease. Other investigators also noted some false reactions in this disease,[81,110,180] but Eagle[71c] did not find any among 13 cases.

Rat-bite Fever. Brown and Nunemaker[35] in 1942 critically reviewed the American cases of rat-bite fever reported up to 1942 and pointed out that adequate proof has been obtained in only few cases, that *Spirillum minus* was the etiologic agent. Of 17 definitely spirochetal cases found in the American literature since 1930, 10 had a positive Wassermann or flocculation reaction. Beeson[15] recently reported 2 more cases due to the spirochete, one of which had several weakly positive Kahn reactions. More recent evidence of the ability of this disease to produce positive reactions is presented by Beeson,[15] by Wooley,[325] and by Taussig.[299] On the other hand, among the older reports, Bayne-Jones[11] deprecated rat-bite fever as a source of false positive reactions. Among 81 patients, 3 of 18 tested yielded positive reactions. Bayne-Jones[11] felt they were syphilitic.

According to Brown and Nunemaker,[35] some cases of rat-bite fever are due to *Streptobacillus moniliformis* (*Streptothrix Haverhillia moniliformis*). Of 8 patients collected from the American literature in whom serologic tests were made, 3 had positive reactions. One of these probably had syphilis, thus leaving only 2 laboratory infections reported by Dawson and Hobby[61] which were insufficiently followed up. Brown and Nunemaker[35] added 8 cases of their own. They made the diagnosis by culture or by a high titer of the antibodies to the streptobacillus. A transient positive reaction was found in only 1 case. These data are insufficient to place this type of rat-bite fever as a real cause of false positive reactions in the serologic tests for syphilis.

Rat-bite fever without specification of cause continues to be reported as a source of false positive reactions.[32,127,206] No reports have been found dealing with the effects of artificial rat-bite fever (Sodoku) used therapeutically, on the development of false positive reactions.

According to Brown and Nunemaker[35] one may conclude that the spirallary form of rat-bite fever is associated in 50 to 60% of patients with a false positive reaction, while in the small number of the streptobacillary cases reported, the false reaction may occur in 37%. Altemeier, Snyder and Howe[1] state that the serologic reactions for syphilis are usually negative in the spirillary form and negative in the bacillary form of rat-bite fever. The fact that penicillin benefits both types does not contribute to the elucidation of the problem of false positive reactions which the other authors cited above have reported as occurring in this disease.

Relapsing Fever. Although this is thought to be a rare disease in the United States,[217] it is a frequent cause of false positive reactions to the serologic tests for syphilis. A complete study of the early literature plus their own experience was reported in 1938 and 1939 by Ts'un and Chung,[304] and Chung and Chang.[47] They found that 7.95% of 88 patients had transient positive Kolmer, Kahn or Kline reactions. These reactions became negative usually within 1 to 3 weeks when the temperature was normal. Serums of 29 cases in which intercurrent syphilis was diagnosed were found to be persistently positive. Those from the rest of the cases were uniformly negative. Pai,[229] at about the same time, reported that 7 of 14 cases in his series gave positive Wassermann reactions which became negative when the disease responded to small doses of arsenicals.

Trypanosomiasis. Although Landsteiner[179] and his associates found that experimental trypanosomiasis of rats and rabbits gave positive Wassermann and flocculation reactions, it is curious that no recent reference to such an occurrence in patients has been found. This experience is concurred in by Davis. Davis reports that Kelser has developed a diagnostic complement fixation antigen for *T. cruzi*. Kelser stated that "tests of numerous Wassermann-positive sera indicate that no difficulty will be experienced from cross reactions in connection with the two diseases."

Kala-azar. There is no unanimity of opinion as to the exact influence of kala-azar on the serologic reactions of the serologic tests for syphilis. Greval and his co-workers[108] believe it is a frequent cause and, in fact, more frequent a cause of positive reactions to the Wassermann test in India than is syphilis itself. Lloyd and his co-workers,[186] however, do not concur. It is interesting to note that an L. E. Napier is involved in the publications of both sides of this question.

Unclassified Infections. Natural or induced fever was responsible for 2.2 to 8.9% positive reactions among 46 cases tested in the first United

States Serologic Evaluation Study.[55] Of the so-called "standard" tests, only the Kolmer and the Hinton gave positive results—2.2 and 2.3% respectively. In the 1941 Washington Serology Conference,[234d] febrile or afebrile intercurrent illnesses yielded mostly 99 to 100% specificity in the standard tests. Afebrile diseases showed in the standard tests that they were 99.3 to 100% specific. Corrigan[50] found 3 positive reactions in 3 non-syphilitic cases of endocarditis. On the other hand, Kelson and White[156] state that syphilis of the nervous system and elsewhere has been diagnosed as the primary disease or accompanying condition in subacute bacterial endocarditis because of false positive serologic tests. Brown and Nagle[34] in 1938 found only 1 positive Kahn reaction among 64 patients with tularemia. This disease undoubtedly has little effect on the serologic reactions. Hydatid cyst of the lung has been mentioned in connection with positive reactions.[99] Weil's disease was shown by Rein and Elsberg[248] to be a frequent cause of positive reactions to the tests for syphilis. Among 87 serums, 38 (43.6%) gave such a reaction. They were usually of low titer. Rein and Elsberg[248] thought that repeated tests in Weil's disease would give a higher percentage of positive reactions. Typhus has also caused biologic false positive reactions. Reynes and Richard[251] reported a case in 1940. Warnecke[311] has also studied this question. Rein and Elsberg[248] studied serums from 104 patients with epidemic and murine typhus and on the basis of single examinations he found 39.4% positive reactions. Undoubtedly here, too, repeated testing might have raised the percentage of false reactions. No statement is specially made, but it is presumed that Rein's cases were non-syphilitic. Rein and Elsberg[248] also tested serums from 53 patients with filariasis. They noted 11.3% doubtful or positive results. A number of authors have reported false positive reactions in various diseases, mostly infections in children.[32,48,127,256]

Jaundice of various types has been rated as possibly inducing biologic false positive reactions. Davis and Sidel[59] found 3 positive reactions among 103 patients with jaundice. Rominger and Szego[253] reported a case of catarrhal jaundice with a false positive reaction. In the first United States Serologic Evaluation Study,[55] however, all the more commonly used tests gave no false reactions among 51 cases of jaundice. Other tests gave as much as 2 to 3.9% positive. Kutzell and Puccinelli[177] observed 15 transient false positive or doubtful positive reactions in 63 patients with infectious hepatitis among allied military personnel in Sicily. These reactions were noted after the appearance of the jaundice, since the serums were not tested prior to the onset of the jaundice.

Non-infectious States. Pregnancy and menstruation have been cited as causing biologic false positive reactions to the serologic tests for syphilis. Spiegler[284] in 1932 found only 0.45% positive reactions among 6580 patients. In the 1934 serology conference,[55] the "standard" tests, with the exception of the Hinton, gave no such reactions in 54 patients. The Hinton test yielded 109% positive reactions. Kandler[152] in 1940 concluded from an experience with 10,354 pregnant women, that there is no evidence that pregnancy impairs the sensitivity or specificity of the tests. Ingraham and Mayer[135] likewise, from a small series of carefully studied normal persons, found that the menstrual cycle has no effect on the serologic reactions for syphilis. *Malignant* tumors have given little evidence that they affect the serologic reactions. In this connection, one must remember the frequent association of malignancy and syphilis. The 1934[55] serology conference and the 1941 Washington conference[234d] yielded little to support the idea that tumors cause false positive reactions.

Sorba,[281] however, found that 14.1% of 262 patients with carcinoma of the cervix gave positive reactions, whereas the usual run of carcinoma patients in the same region gave 1.6% positives. While these are not claimed to be false reactions, one wonders whether carcinoma of the cervix predisposes to false reactions. Matsumura[198] in 1934 tested the serologic reactions in 397 cases of malignant tumors (336 carcinoma, 61 sarcoma of various parts of the body). The reaction was positive in 13% of the carcinoma and about 20% of the sarcoma patients. No clinical evidence of syphilis was found in many of these patients, even at autopsy.

Horse serum has been known to produce biologic false positive reactions.[24,91a,126,286,318] Other rarely mentioned causes of reactions are: lead poisoning, acetic acid poisoning, diabetes, drugs (*e. g.*, sulfanilamide), ether anesthesia, repeated blood donation,[300] cadaver blood.[290] The verity of these as producers of false positive reactions is highly problematical.

Hyperproteinemia. In connection with certain diseases which yield presumably false biologic reactions, the question of hyperproteinemia has been raised. Certain aspects of this subject have been discussed elsewhere in this review (*e. g.*, lymphogranuloma venereum). A general review of the relationship of hyperproteinemia to biologic false positive reactions of syphilis has been the subject of special study by Cardon and Atlas.[40] They noted that hyperproteinemia, except when caused by dehydration, is associated almost invariably with highly elevated sedimentation rates, even in the absence of fever. Jeghers and Selesnick[140] observed anticomplementary Wassermann reactions frequently in association with hyperproteinemia, especially in patients with such conditions with lymphogranuloma venereum and multiple myeloma. Cardon and Atlas,[140] comparing the conditions reported with hyperproteinemia with those presumed to give biologic false positive or anticomplementary reactions, suggest that perhaps a common factor is concerned.

While the reasoning of these men is suggestive and the association of hyperproteinemia with biologic false reactions frequent, Cardon's group[40] used criteria of falseness which of themselves are false, namely, the presence of a positive Kahn reaction but negative Wassermann reaction (in 2 cases anticomplementary). They considered 1 patient who had simultaneous positive reactions to both tests as syphilitic. Davis[57] stated that the impression that false positive serologic reactions are often caused by conditions which give rise to a marked hyperglobulinemia is unwarranted. He stated: "Hyperglobulinemia is in general caused by two types of disease: (1) a variety of infections, in which at least part of the increased globulin is antibody; and (2) conditions not especially involving antibodies, such as cirrhosis of the liver, dehydration and multiple myeloma. There is reliable evidence that any member of the second group is associated with these positive tests; it appears reasonable to regard the hyperglobulinemia and the occasional positive reactions of the first group as separate manifestations of the underlying infectious process, rather than to consider one the cause of the other."

Holmberg and Gronwall[129] reported that a peculiar crystallized serum globulin from a patient with an undiagnosed arthritis was reported anticomplementary like other isolated globulins.[58]

False Positive Reactions in the Cerebrospinal Fluid. The occurrence of false positive serologic reactions for syphilis in the cerebrospinal fluid has received little attention, although as far back as 1910 Oppenheim[227] reported the first example of angle tumor (pontocerebellar) with positive cerebrospinal fluid Wassermann. In many of the subsequently reported

cases technical error has not been excluded by confirmation of the original positive reaction nor has syphilis always been definitely excluded. Recent authors[71e,210b] have implicitly relied on the specificity of the cerebrospinal fluid Wassermanns except, perhaps, "in the rare instances in which a syphilitic patient with a positive blood Wassermann develops an acute pyogenic or aseptic meningitis. This phenomenon undoubtedly depends on an alteration of the blood-spinal fluid barrier and a passage of reagin from blood to spinal fluid." Although some authors agree with the idea that false positive reactions represent transfer (filtration) of reagin from the blood, there is evidence that the reagin or antibody is formed within the central nervous system locally.[12b,93,144,214,319a,b] The chief argument of those who favor the filtration theory is that there is rarely more reagin in the cerebrospinal fluid than in the serum. Wiener and Derby[319b] have shown that while it is true that the reagin content of the cerebrospinal fluid is hardly ever greater than that of the serum, this is not a valid argument for Dujardin's theory.[68] Were the concept of passive filtration correct, a parallel filtration of iso-agglutinins could be expected, but in no case could Wiener and Derby[319] find any iso-agglutinins in the cerebrospinal fluid, even when the reagin titer was equal in blood and cerebrospinal fluid and the iso-agglutinin titer in the blood higher than that of the reagin. Wiener and Derby[319] do not imply that there is never any filtration of reagin from the blood into the cerebrospinal fluid. They further explain the lower titer of reagin in the cerebrospinal fluid on the basis of the usually less poorly developed capacity of the central nervous system to form antibodies, possibly because of its small number of reticuloendothelial cells. If the Ehrich and Harris theory[75] of antibody formation in the lymphocytes is correct, Wiener and Derby's contention[319] would still seem to hold.

Further evidence for the idea of local formation of reagin in the central nervous system in neurosyphilis is suggested by the work of Kabat and co-workers[144] who demonstrated a high proportion of gamma globulin in such fluids which could not be explained on the basis of filtration from the blood. The question of faulty absorption of the spinal fluid which may produce a local concentration of the proteins has apparently not been explored. Freund[93] as well as Morgan, Schlesinger and Olitsky[214] have shown that a lower titer of various antibodies develops in passively immunized rabbit's cerebrospinal fluids as compared with the serums. Therefore, aside from cerebrospinal fluids grossly contaminated with positive blood[86,189,279] in sufficient quantity to induce a technically false positive reaction in the fluid, fluids otherwise technically correct would rarely, if ever, yield false positive reactions. In spite of this, a large literature has arisen purporting to demonstrate such reactions. Furthermore, to prevent non-specific and prezone reactions in the Wassermann test with sera and spinal fluids, Boerner and Lukens[27] advised the use of egg albumen as a protection protein. Later, however, Boerner, Lucas and Ellis[26] found the addition of egg albumen to cerebrospinal fluid in the Boerner-Lukens method of Wassermann test had a desensitizing effect when pretested complement was used. They recommend avoiding the addition of egg albumen to cerebrospinal fluid if the complement is pretested with the antigen used.

A few reports of false positive cerebrospinal fluids have been made in mumps,[277] in malaria[160,322] and in neurologic diseases.[64,142,181,200,213,256,271] Kuske,[176] on the other hand, investigated the frequency with which complement fixation tests for syphilis with cerebrospinal fluid from patients

given malaria treatment for gonorrhea became positive. None of these patients developed positive reactions in the cerebrospinal fluid. He also found that positive Wassermann reactions did not develop in the cerebrospinal fluid of patients with latent syphilis during malarial infection.

Among the neurologic diseases which have been reported as associated with false positive cerebrospinal fluid reactions (with negative blood reactions), encephalitis,[213] post-traumatic convulsions,[142] meningococcus meningitis,[32] pneumonia and meningitis[256] are included. McLean and Munger[200] report 10 cases in which the cerebrospinal fluid gave biologic false positive reactions for syphilis. These consisted of encephalomalacic atrophy, encephalomalacia, streptococcus septicemia, electrical burn, extrathecal panniculitis, cerebrospinal rhinorrhea, skull fracture, concussion, neuritis and multiple sclerosis. The authors produced a positive Wassermann reaction in the cerebrospinal fluid of a dog by injecting intracisternally the fluid from a craniopharyngioma.

Sézary and Terrasse[271] have summarized the literature on false positive reactions associated with tumors of the neuraxis. They added 4 cases of their own to the world's literature (32 in all). Seven of the patients were old syphilitics, but in 25 there was no evidence of syphilitic infection. In most of the cases, the Wassermann was strongly positive. Among 29 cases in which the blood Wassermann was examined, the reactions were positive in 4, slightly positive in 2, and negative in 23. A positive reaction in cases of brain tumor is rare (7 of 40 cases, Vincent[307]). The sites of the tumor seem to have little influence on the outcome of the serologic reaction except that tumors which block the subarachnoid space and cause Froin's syndrome are especially apt to cause this anomaly. Antisyphilitic therapy may often bring about temporary improvement in the brain lesion. The positive reaction in the cerebrospinal fluid in brain tumor is also sometimes accompanied by hyperalbuminosis and hyperleukocytosis. We have seen cases of neuraxis tumors which confirm these findings of a positive Wassermann reaction and excessive protein content of the cerebrospinal fluid. Desneux[65] and, more recently, Cardona[41] have denied that positive Wassermann reactions occur in the cerebrospinal fluid in cases of nervous system tumors in the absence of syphilis.

A most interesting and important contribution to the problem of biologic false positive cerebrospinal fluid Wassermann reactions is that of Scott, Reynolds and Mohr[269] dealing with such reactions associated with meningitis. These workers have shown in a convincing fashion, on the basis of 7 cases of confirmed false positive cerebrospinal fluid Wassermann reactions in non-syphilitic individuals during the course of meningitis (3 tuberculous, 2 meningococcal, 2 aseptic lymphocytic), and on 20 unconfirmed positive cerebrospinal fluid Wassermanns in non-syphilitic patients with various types of acute intracranial disease (technical errors?) that false positive cerebrospinal fluid Wassermann reactions may occur in syphilitic and non-syphilitic patients during the course of pyogenic, aseptic, and tuberculous meningitis, and perhaps other types of intracranial disease. They conclude that the diagnosis of neurosyphilis based on a positive cerebrospinal fluid Wassermann reaction alone is unjustified in patients suffering from meningitis and other acute intracranial disorders until repeated examinations, performed after these processes have subsided, demonstrate the continued presence of reagin. With this view we are in full accord.

Kolmer,[165e] discussing this problem, concludes that cerebrospinal fluids are much less likely than sera to yield these false reactions. This, he

believes, is due in a large part to technical conditions, but it is unlikely that normal non-syphilitic individuals yielding falsely doubtful and positive reactions on the blood also show a similar reaction in the spinal fluid. It is well known that the natural antibodies occurring in the sera of normal individuals do not occur in their cerebrospinal fluids.

The Possible Causes of the False Positive Reactions. At the outset of any discussion of this phase of the problem, one may state categorically that there is no definite knowledge as to the mechanism responsible for the production of biologic false positive reactions to the tests for syphilis. Any proposed explanation is countered by evidence "proving" just the contrary. In view of the conflicting and often almost incomprehensible theories of the underlying mechanism of production of not only the false but the true serologic reaction, it is our purpose here only to refer the reader for details to the appropriate publications. Moreover, throughout this presentation, some discussion has been made of some of the points dealing with probable mechanisms.

Davis[57] has conveniently classified the possible causes of biologic false positive reactions as follows: "(*a*) an antibody identical with the Wassermann antibody produced in syphilis; (*b*) an antibody differing in some ways from the true Wassermann antibody, but cross-reacting with Wassermann antigen or some component thereof; or (*c*) physio-chemical changes not involving antibodies, which produce flocculation or complement fixation reactions."

The nature of syphilitic antibodies has been recently discussed in detail by Eagle,[71a,d,e] Eagle and Hogan,[72] Witebsky,[324] Beck,[12c] Kolmer,[165a] Davis,[57] Ratcliffe,[244] and Sachs.[259] The review of this subject by Davis[57] and his proposals for future study of the fundamental processes involved in the problem of biologic false positive reactions are worthy of extended study.

Spirochetal Antigens in the Serum Diagnosis of Syphilis. Antigens prepared from cultures of *Treponema pallidum* have recently aroused considerable interest and a hope that they might serve as a specific means of differentiating true from biologic false positive reactions to the serodiagnostic tests for syphilis, as well as help to explain the basis for these reactions. This work, revived in this country by Erickson and Eagle[78] has been thoroughly restudied by Kolmer and his group in a series of exhaustive publications.[165a,f,g,h,i,169a,b,172] Unfortunately the use of spirochetal antigens does not supply the answer to the specific *versus* the nonspecific reaction question. But, because of the fundamental problems involved, it is proposed to review the significant facts regarding spirochetal antigens.

Antigens prepared from cultures of *T. pallidum* were first employed in 1912 by Noguchi,[225] and Craig and Nichols,[53] and in 1913 by Kolmer, Williams and Laubaugh.[172] At that time these antigens were found to be inferior in sensitivity to alcoholic extracts of beef heart reinforced with cholesterol in the Wassermann test. In 1929 the work of Gaehtgens[94b,c] and Gaehtgens, and Otto[94a] renewed interest in spirochetal antigens, prepared of cultures of the Reiter strain of *T. pallidum*. This was followed by a large literature on the use of this antigen, which was commercially available in Germany as "palligen" and other spirochetal antigens. For a complete critical review of this literature the reader is referred to the excellent paper by Kolmer.[165f] Kolmer, Kast and Lynch[169b] found, however, that antigens prepared of cultures of *Treponema microdentium* and *T. macrodentium* are capable of fixing complement with syphilis reagin just as well as those prepared of cultures of various strains, of *T. pallidum*,

including the Reiter strain. That is to say, complement fixation reactions with spirochetal antigens in syphilis are of a group character. Kolmer, Kast and Lynch[169b] also found the same to be true of agglutination of these spirochetes by normal and syphilitic serums. Kolmer and Kast[168] suspect on the basis of cultural characteristics that the Reiter strain may not be *T. pallidum* at all.

In spite of the claims that spirochetal antigens are specific, it has been well demonstrated that antigens prepared of cultures of alleged *T. pallidum* are capable of giving a varying percentage of non-specific or falsely positive complement-fixation reactions with the sera of non-syphilitic individuals.[169a] In a total of 36,255 tests employing "palligen" these have varied from 0.4 to 3.4%.[165ag] In fact, Erickson and Eagle[78] reported the 3.4% false positives in the serums of 528 non-syphilitic individuals although none were observed in the serums of 15 additional individuals who were normal.[72] In the 1941 Washington Serology Conference,[234d] Richter found that the Kolmer simplified tests conducted with an antigen of the Reiter strain gave 6.3% positive or doubtful reactions with the serums of normal individuals and non-syphilitic patients, excluding those with leprosy and malaria. In the same survey Eagle[71f] found 1.9% positive or doubtful reactions on the same group with a spirochetal antigen likewise prepared of the Reiter strain. With both antigens, the percentage of these falsely positive reactions with the serums of non-syphilitic individuals was higher in the case of those with febrile intercurrent diseases, tuberculosis and malignant disease than in normal individuals. The antigen likewise yielded high percentages of positive reaction in serums from patients with malaria and especially leprosy just as non-specific reactions occur in the serums of patients with these diseases when tested with the Wassermann or flocculation tests. In the Washington Conference Richter reported 57.6% positive or doubtful reactions with the serum of lepra patients tested by the Kolmer simplified method using tissue antigen and 27.1% positive or doubtful reactions with the Kolmer spirochetal antigen. The Eagle Wassermann test gave 39.8% and his pirochetal antigen 20.6% positive or doubtful reactions. These figures argue very potently against Eagle and his colleagues' claims that the use of spirochetal antigens will identify as biologic false reactions the positive Wassermann and flocculation reactions encountered in leprosy and malaria. Kolmer interprets these results to mean that in the serums of some non-syphilitic human beings there is a natural spirochetal antibody capable of yielding falsely positive reactions to the complement fixation as well as flocculation procedures, not only with suspensions of cultures of "alleged *T. pallidum* but with other spirochetes as well with special reference to *T. microdentium* and *T. macrodentium*." While this natural antibody may occur in serums it does not occur in the cerebrospinal fluids of non-syphilitic persons.[169a] This is in keeping with the well-known fact that natural antibodies like antitoxins, agglutinins, etc., commonly present in normal serums, do not occur in normal cerebrospinal fluids. Accordingly Richter and Eagle did not find any non-specific or falsely positive complement fixation reactions with cerebrospinal fluids of non-syphilitic individual tests with spirochetal antigen in the Washington survey.

Kolmer, Kast and Lynch[169a] also found that the acquired antibody in syphilis is more likely to give positive complement fixation reactions with antigen prepared of virulent *T. pallidum* (Nichols-Hough strain) recovered from acute testicular syphilomas of rabbits than with antigens prepared of cultures of non-virulent *T. pallidum*. Technical difficulties of securing

the tissue spirochetes free of cellular débris make it unlikely that tissue spirochetes can be used on a large scale. A culture of virulent *T. pallidum* has not as yet been obtained[168] even by the newer methods of chick embryo[228] or tissue culture.[168,320]

The question is unanswered as to whether or not spirochetes contain an ubiquitous lipid also present in alcoholic extracts of beef heart with the result that the various serologic tests are due to spirochetal antibodies as maintained by Eagle and Hogan.[72] Kolmer, Kast and Lynch[169] showed by absorption experiments that the reagin responsible for the Wassermann and flocculation reactions in syphilis is different from the antibody producing positive reactions in these tests with the spirochetal antigen. This view is affirmed by Kroó, Schultze and Zander,[175] Gaehtgens,[94e] and by Beck.[12c] Beck reached this conclusion concerning the independence of the 2 types of reagin by observing that the absorption of syphilitic serum with Wassermann antigen removed the reagin but not the complement-fixing antibody or agglutinin for the Reiter strain of *Spirochæta pallida*. On the other hand, absorption with spirochetes removed all of the reagin. Absorption with an alcoholic extract of the Reiter strain of spirochetes removed the reagin but not the spirochetal antibodies. This showed a relation between the lipids, of the spirochetes and the lipids of the Wassermann antigen (alcoholic extract of heart). Eagle and Hogan[72] have reported that absorption of human syphilitic serum with beef heart lipids removed all of the reagin but not the spirochetal antibodies. This accords with the experience of Kolmer[165g] and Beck.[12c] But Eagle and Hogan[72] reported that absorption with the Reiter strain of spirochetes ("palligen") removed not only the spirochetal antibodies but the reagin as well, in contrast with the results of Beck and Kolmer. As a result of their experiments Eagle and Hogan[72] concluded that spirochetes contain an ubiquitous lipid, also present in alcoholic extracts of beef heart and that the Wassermann, flocculation and spirochetal complement fixation reactions are due to spirochetal antibodies. Kolmer has disagreed with this view and in addition maintains that immunization of rabbits with living and heat-killed strains of *S. pallida* (Nichols-Hough; Noguchi; and Kroó) as well as with *T. microdentium* and *macrodentium* produced large amounts of spirochetal antibodies but not the reagin "lipoid antibody."[169a] Kolmer considers the question whether rabbits given injections of tissue lipids produce reagin and spirochetal antibodies as undecided.[13,72,165a,260] Beck[12c] furthermore noted that when human syphilitic serum is heated at 63° C. for 30 minutes the spirochetal antibody is not destroyed but the Wassermann reagin is. Eagle and Hogan[72] found no difference in thermoresistance while Kolmer, Rule and Trist[171] found that heating serum 30 minutes at 62° C. results in a definite loss of Wassermann antibody. Kolmer found a lesser loss in the case of the spirochetal antibody. In the case of normal rabbit serum, Kolmer found striking differences in resistance to heat between the substance yielding positive Wassermann reaction and spirochetal antibody. The former is destroyed at 62° C. while the spirochetal antibody is resistant. It is possible that this Wassermann reactive substance in normal rabbit serum may not be identical with human syphilitic reagin. It is concluded that the preponderance of evidence favors independence of the spirochetal antibody and syphilis reagin.

The mode of action and the chemical nature of spirochetal antigen is unknown. It is probable, according to Kolmer and his associates[172] and to Beck,[12c] that the lipids of *T. pallidum* are important in complement fixation by the Wassermann reagin. Whether spirochetal antibody

reacts with them is unknown; but it has been suggested that it fixes complement with some other constituent of spirochetes of a non-protein nature.[169b]

The value of spirochetal antigens as a differential test seems to the Reviewer to be questionable. In the Washington Survey, Richter, using Kolmer's simplified test with tissue or lipoidal antigen had a sensitivity rating of 74.1% and the Kolmer spirochetal antigen 70.6%. The rating for the Eagle Wassermann test was 59.2% and for his spirochetal antigen 75.9%. Kolmer also found that a mixture of spirochetal and tissue or lipoidal antigens was more sensitive in complement fixation tests with syphilitic sera than spirochetal antigen alone, but less sensitive than tissue or lipoidal antigen alone. The mixture has also given a smaller percentage of non-specific or falsely positive reactions with normal serums than the spirochetal antigen alone.

Verification Tests. Shortly after the complement fixation and flocculation tests were found to be non-specific, a number of laboratory procedures were devised to differentiate between true and false positive reactions. Hecht[121] in 1914 proposed the first of these so-called verification or confirmation tests. This was followed in 1921 by that of Wassermann[314] which was based on an alleged separation of antibody from antigen by filtration. Witebsky[324] in 1933 obtained purified antibody from a malarial serum as well as from syphilitic serum by a method of heat dissociation but he failed to recover any from certain other false positive serums. Others have also proposed differentiation tests which have proven to be of little practical value.

In 1940, R. L. Kahn[146] showed that: (1) Serums from syphilitic persons giving positive reactions with a diagnostic test show by means of a special procedure a tendency toward marked precipitation at 37° and little or no precipitation at 1° C. The procedure is similar to that of the Kahn test. (2) Serums from apparently normal animals and from presumably non-syphilitic persons giving positive reactions with a diagnostic test show by the same procedure a reverse tendency, namely, marked precipitation at 1° and little or no precipitation at 37° C.

These observations suggested the practical utilization of this procedure. Thus, when a serum gives a positive reaction with a diagnostic test and this reaction is suspected of being a false positive, the serum is examined with this procedure at 37° and 1° C., respectively. If precipitation is found to be marked at 37° and is negative or practically negative at 1° C., the probability is that the diagnostic test gave a correct reaction. If, however, precipitation is found to be marked at 1° and is negative or practically negative at 37° C., the probability is that the diagnostic test gave a false reaction.

The term "verification test" has been applied to this differential temperature procedure. The test is reported positive or negative, depending on whether the serum tested gives more marked precipitation at 37° or at 1° C. In the case of strongly positive serums, the degree of precipitation is not affected by temperatures of 37° or at 1° C., unless they are first diluted with physiologic salt solution. The extent of dilution necessary is determined by the quantitative Kahn test. After thus reducing the serums from strongly to weakly positive, the differences in the results at the two temperatures become evident.[149]

Application of the Kahn differential temperature verification test to the problem of the biologic false positive reaction has led to a variety of differing opinions. Chargin and Rein[46] in their appraisal of this test on

clinical and serologic grounds on 1565 patients with various conditions comprising syphilis and various dermatoses, questionable conditions, pregnancy, contagious conditions, found that among 349 syphilitic patients who had received varying amounts of treatment, the verification tests gave the syphilitic type of reaction in 100% of those with strongly positive serodiagnostic reactions, in 76.5% of those with weakly positive reactions and in 40.2% of those showing doubtful reactions. There were no reactions of the syphilitic type in the patients with negative serodiagnostic reactions. The general biologic type of reaction in the group with negative serologic reactions was 7.1% and in the group with doubtful serologic reactions 12.1%. In the non-syphilitic groups a varying percentage of syphilitic and general biologic types of reaction was noted. It would appear therefore that strongly positive serums regularly give the syphilitic type of reaction but weakly positive serums, syphilitic or not, tend to give the other type of reaction. Green and Forster[100] have indicated from their study that the usefulness of the verification reaction lies in the diagnosis of syphilis no less than in the recognition of falsely positive reactions. Beveridge[21] also felt that the verification test gives a great increase in sensitivity apart from its verification aspect. In 268 patients with pinta, all of whom gave strongly positive serodiagnostic reactions, Chargin and Rein[46] found 83.9% gave a syphilitic type of reaction to the verification test. Briceno Rossi,[31] however, found that in general the test gave a syphilitic type of reaction in pinta and yaws. The syphilitic type of verification reaction has been reported in some serums from patients after vaccination (Lubitz;[190] Lynch, Boynton and Kimball;[193] Thomas and Garrity[302]). Of 30 lepers Briceno Rossi[31] found 19 to give negative verification reactions; 4 positive at 1° C., and 37° C.; 3 gave the syphilitic type and 4 the general biologic type of result. Chargin and Rein[46] found essentially the same degree of unreliability of the test in leprosy. The test has even been accepted and recommended for routine use in malarial districts.[44,138] Kahn[146] soon recognized the shortcomings of his heat test and in 1942 proposed a new verification method. This consists in carrying out a standard Kahn test parallel with a similar test in which the antigen suspension is prepared by mixing the antigen with 2.5% sodium chloride solution instead of the 0.9% salt solution, and also one in which the serial dilutions are made with distilled water. A higher quantitative titer on serial dilution with 2.5% salt concentration than 0.9% salt concentration denotes a general biologic (non-syphilitic) type of reaction. In the presence of the latter type of reaction the titer with serial dilutions of distilled water is still higher than that with the serial dilutions of 0.9% salt solution. This type of verification test has not had wide usage.

Kahn[146d] apparently induced by Chargin and Rein's[46] evaluation of the heat differential test has added a third test to the second "salt dispersibility technique" which he has designated "Method B." This consists of performing the standard Kahn test as usual with the exception that, after the 3 minutes shaking period, sodium chloride solution of 2.5% concentration instead of 0.9% is added to the tubes in the regular amounts of 1, 0.5 and 0.5 cc., respectively. If a physician submits a specimen for verification the following procedure is followed: (1) A standard Kahn test is performed; (2) "Method B" is carried out; (3) the salt dispersibility technique is done. In the case of weakly positive and negative reactions, the "heat differential" test is applied while in the case of strongly positive results, the "triple quantitative technique" is employed. An excellent critique of the so-called "verification" tests with particular reference to

the various Kahn tests is given by Mohr, Scott, Hahn, Clark and Moore.[207] One must agree with these authors—that the "serologic phenomena noted by Kahn are of the greatest importance for further detailed scientific investigative study. It is clearly of fundamental concern to determine whether the positively reacting substance occurring in certain (perhaps all) normal human beings or produced after intercurrent infections or other stimuli, is qualitatively identical with the reagin produced in syphilis. To apply these phenomena to a diagnostic test, designated by so great an authority as Kahn as a "verification test," is, however, distinctly premature on the basis of present information."

Rytz[258] proposed a differential test in 1939 involving the principle of removing the bulk of serum protein by precipitation with 2% copper sulfate solution and leaving in solution the reacting substance of syphilitic serum. In spite of repeated progress reports by Rytz,[258] no concerted attempt to verify the performance of this procedure has developed.

Neurath and his associates[223] at Duke University in an extensive investigation directed toward the development of a serodiagnostic method for the differentiation between syphilitic and non-syphilitic sera, made observations which indicate that in the 2 groups of sera the reactive antibodies differ from each other in certain significant respects. Based on the previously reported work which showed that even in strongly reactive syphilitic sera the antibodies constitute but a minute fraction of the total proteins and that isolation by specific flocculation with lipoidal antigen yields extremely low recovery of the purified product, a practical approach to the problem was attempted by this group based on nonspecific methods of characterization and fractionation of the sera. Results with electrophoresis, fractionation, inhibition, and redispersion, heat stability and adsorption in calcium phosphate indicate that the antibodies of truly syphilitic serums reactive with lipoidal antigen, differ from those of biologic false positive serums in certain chemical and immunologic respects. These investigators are exploring the possibility of adapting these findings to the development of a practical method of differentiating true from false positive reactions to the tests for syphilis. Rein and Pillemer[247] tried an "inhibition procedure" for differentiating true from false reactions but they found the method to have definite limitations.

Requirements of a Satisfactory Differential Test. Rein and Elsberg[248] have outlined under the following heads the criteria a verification procedure must fulfill before it can be considered practical.

> "1. Serums from syphilitic individuals with positive serologic tests should always give a syphilitic type of verification reaction.
> "2. Serums from non-syphilitic individuals with positive serologic tests should always give the false positive type of verification reaction.
> "3. The diagnosis of syphilis should be established in persons who consistently give the syphilitic types of verification reaction on repeated examination.
> "4. The diagnosis of syphilis should be excluded in persons who consistently give the biologic false positive (non-syphilitic) type of verification reaction on repeated examination."

Whether or not newer differentiating methods will yield reliable information is a question. In 1943 Kahn[146f] still maintained that with his verification tests their greatest value lay "in the investigation of the specificity of positive serodiagnostic reactions in such cases in which all clinical indications point to the absence of syphilis." Rein and Elsberg[248] are

not so certain that too much confidence can be "placed in the verification test results in those individuals whose syphilitic status is in doubt." The Reviewer's limited experience agrees with this latter viewpoint.

Management of a Suspected Biologic False Positive Reaction. Since there is no satisfactory single procedure or combination of laboratory procedures as yet available to differentiate with certainty between true and false reactions to the tests for syphilis, various compromise clinical and laboratory work-ups have been suggested. In 1926 Stokes[289a] cited a series of 22 procedures which might have to be invoked in reaching a decision as to whether or not a patient has syphilis. In 1939 he proposed a scheme for the checking of a positive serologic test report.[289b] This was followed in 1940 by a brief outline of a procedure for the attempted differentiation of these two types of reactions by Moore[210a] and later this was elaborated by Moore, Eagle and Mohr.[211] Other, but somewhat similar, methods of procedure were suggested by Harrison and Osmond,[116] by Kolmer,[165f] by Rein and Elsberg,[248] and by Davis.[57] All these schemes have the same defect; none of them even if followed precisely will really differentiate a true from a biologic false positive reaction. Since, however, they represent the best method of approach to the problem we possess, the method[211] is outlined briefly. For details, the reader is referred to the original sources.

Moore and his associates[211] have suggested the following procedures when biologic false positive serologic tests for syphilis are suspected: careful history; careful physical examination for evidences of acute infection preceding the questionable serologic test, with special reference to lymph nodes, spleen and lungs; search of blood smears for malarial parasites; blood smears for infectious mononucleosis; blood test for heterophil antibody (the Paul-Bunnell test, which is specific for infectious mononucleosis); determination of the sedimentation rate; repetition of the serologic test for syphilis by several different techniques and in several different laboratories; performance of a "verification test;" testing the patient's serum by complement fixation with spirochetal antigen; testing the patient's serum with wholly non-specific antigens such as those prepared from bacteria; prolonged serologic follow-up; examination of the members of the family and sexual contacts; examination of the cerebrospinal fluid, if a decision cannot be reached earlier. These authors consider the provocative procedure worthless. They advise withholding antisyphilitic treatment unless and until the diagnosis of syphilis is proved.

The occasional occurrence of false positive reactions should not lead to wholesale condemnation of the serologic tests for syphilis. The following quotation from Harrison and Osmond[116] is a sound evaluation of the present status of these procedures.

"In 1918 the Medical Research Committee's (now the Medical Research Council) Committee on the Standardization of Pathological Methods said:

"'*In the opinion of the Committee there is no process of biochemical diagnosis that gives more trustworthy information or is liable to a smaller margin of error than the Wassermann test when it is performed with completeness and with proper skill and care.*'

"This is probably as true today as it was when written a quarter of a century ago, but it is equally true that no group of tests has given rise through unskillful performance and through inadequate appreciation of their limitations, to more unhappiness than have the serum tests for syphilis."

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ADDENDUM

Since the foregoing material was prepared, the continuing interest in the subject of biologic false positive serologic reactions to the tests for syphilis is indicated by the appearance of new studies.

Elmes and Findlay (J. Roy. Army Medical Corps, **84**, 29, 1945) studied the Kahn test in 80 British soldiers serving in a hyperendemic malaria zone and suffering from malignant tertian malaria, and found that 23 of them gave at some period a positive reaction. Only 1 of the patients gave evidence of syphilis. The authors call attention to the 1940 version of the Kahn verification test as a possible means of differentiating syphilis from malaria.

The influence of malaria on the cerebrospinal fluid Wassermann reaction as well as the incidence of biologic false positive reactions in the blood Kahn and Wasser-

mann tests was made the subject of a study by Potter, Bronstein and Gruber (J. Am. Med. Assn., **127**, 699, 1945). They found in 100 consecutive male patients with naturally acquired malaria that none yielded positive reactions to the cerebrospinal fluid Wassermann test but 12% of the men had positive blood reactions and 10% had doubtful reactions. This indicated to the authors that the factors which produce the false results in the blood are not present in the cerebrospinal fluid. This study also emphasizes that a diagnosis of syphilis should not be made on the basis of a single test at any time. After an acute attack of malaria, at least 1 month should elapse before taking blood for further testing. In a rejoinder to this report, Brandt (J. Am. Med. Assn., **128**, 152, 1945) calls attention to unpublished observations on patients inoculated with a strain of *Plasmodium vivax* acclimatized to transmission from man to man. Every case became seropositive after the sixth fever bout, but every case became seronegative again within 8 weeks after termination of malaria; the most sensitive test (Wassermann with R. Mueller's antigen) became positive sooner and stayed so longer than less sensitive ones. (Meinicke's earlier methods and the Sachs-Georgi reaction.) Because the Henry test (Arch. Inst. Prophylac., **1**, 341, 1929) in inoculation malaria (Brandt, R., and Horn, L.: Klin. Wchnschr., **14**, 1538, 1935) yields a curve of reactions from negative to positive, to negative, which closely resembles the curve of the non-specific reactions for syphilis, and as Henry describes the behavior of his test in malaria disease just the way Brandt and Horn found it in inoculation malaria, Brandt suggested that one may expect the same parallelism in the non-specific reactions, meaning that a certain time after cessation of fever attacks, malaria does not produce such reactions. A negative Henry test, therefore, by indicating that the period of manifest malaria infection has passed, would enhance the dependability of a positive serologic reaction to the tests for syphilis, where malaria has to be taken into account. From extensive studies of patients (former Austrian soldiers) with a history of malaria, there was no evidence to indicate that beyond the stage of attacks malaria has any influence on the outcome of the serologic syphilis reaction.

Rein and Elsberg (Am. J. Syph., Gon. and Ven. Dis., **29**, 303, 1945) presented a detailed report on the effect of smallpox vaccination on the serologic reactions. They used a serologic battery: Kline diagnostic, Kline exclusion, flocculation tests, and the Kolmer complement fixation test. An attempt was made to do weekly tests on their patients (in some cases 8 to 12 days elapsed between the repeated examinations). The subjects received in addition to the smallpox vaccination, injections of tetanus toxoid and typhoid vaccine on the same day; a second dose of typhoid vaccine the following week; a third typhoid vaccination the 3rd week; a second dose of tetanus toxoid the 4th week; and a third dose of tetanus toxoid the 7th week. Of 129 individuals who developed a vaccinoid or vaccinia reaction, 58 (44.9%) showed doubtful or positive serologic reactions to the tests for syphilis. Of this group, 50 (86.2%) developed their first positive serologic reaction between the 8th and 14th day following the vaccination. Of 80 individuals who developed vaccinia reactions, 41 (51.2%) showed false positive serologic reactions, whereas 49 individuals developed vaccinoid reactions, of whom more than 17 (34.7%) showed false positive reactions. This indicates the possibility that false positive reactions occur more frequently in patients in the vaccinia group than in the vaccinoid group. There was, however, no correlation between the incidence and titer of the false positive reactions and the severity of the skin reaction to the vaccine virus. In the immune reactor group, 36 patients (13%) developed doubtful serologic reactions to one or more tests. Revaccination of a small group (after 3 years) yielded no false positive serologic reactions. A group of 20 patients which was given only typhoid immunization, and another group of 16 patients receiving only tetanus toxoid injections, yielded no false positive reactions. This type of material merits continued investigation because of the serious medical and psychologic import of positive serologic reactions in military personnel.

Hegglin (J. Am. Med. Assn., **129**, 150, 1945), reemphasizes the problem of pneumonia with a positive Wassermann reaction.

In addition to the study of the incidence of false positive reactions to the tests for syphilis, modification of technique, new tests or evaluation of tests, designed to diagnose false reactions have continued to hold the attention of investigators.

Brown, Kolmer and Lynch (Am. J. Syph., Gon. and Ven. Dis., **29**, 200, 1945) have studied the effect of sodium hydroxide on biologic false positive and anticomplementary serologic reactions in syphilis. They found the addition of 0.1 cc. of N/3 or N/4 solutions of sodium hydroxide to 1 cc. of serum before heating at 55° C. has proved effective in preventing biologic false positive Kolmer, Kahn and Mazzini reactions in serum of normal rabbits, in presumably non-syphilitic individuals with malaria, infectious mononucleosis, and virus pneumonia. Less effective results were observed with the serums of presumably non-syphilitic epers. In contrast with the other diseases, N/4 sodium hydroxide yielded more effective results in leprosy than did N/3 sodium hydroxide. Addition of the alkali to syphilitic serums before heating results in the inactivation or destruction of some of the syphilitic reagin but false negative reactions are apt to occur in the Kolmer test only in the case of serums containing small amounts of reagin. The addition of N/3 or N/4 sodium hydroxide to rabbit and human serums has proved effective in the prevention of the anticomplementary reactions in the Kolmer complement fixation test.

Cooper (J. Invest. Dermat., **6**, 109, 1945; Proc. Soc. Exp. Biol. and Med., **57**, 248, 1944) made an electrophoretic study of syphilitic serums and attempted to identify the serum fraction carrying syphilitic reagin. He showed that there are characteristics and significant alterations in the serum proteins after infection in syphilis. There is an increase in all of the electrophoretic globulin fractions which occurs soon after infection and persists throughout the course of the disease in the absence of adequate treatment. In some cases of apparently false positive serums, the changes found in syphilis do not occur. The reagin for the Kahn and Wassermann reactions has been shown to occur in the γ globulin fraction. In the 1944 study, Cooper stated that the β or γ globulin fractions, or both, had been identified as carriers of the Wassermann and Kahn reagins.

Rein and Elsberg (J. Invest. Dermat., **6**, 113, 1945) ask whether the current veri ication tests are of practical value in the serodiagnosis of syphilis. After an exhaustive and careful analysis of the confirmation or verification tests and the addition of an unpublished, original method (Rein-Pillemer), they conclude that none of the methods presented has been able to distinguish consistently between true and false positive serologic reactions. There is an urgent need for a procedure which will perform this differential function and the authors suggest that any new procedure should be subjected to critical evaluation by a selected committee of serologists and clinicians before it is proposed to and by the medical profession at large.

OTO–RHINO–LARYNGOLOGY

UNDER THE CHARGE OF

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CANCER OF THE MOUTH: ITS PRESENT DAY TREATMENT

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Of the cancer deaths in the United States 3% are malignant tumors of the mouth.

Studies of the statistics of men who have had a wide experience in oral cancer and who have not been biased in their opinion as to the use of either radiation or surgery show a high incidence in 5 year "cures" in mouth cancer—the percentage of cures ranking only below skin and breast cancer, in the hands of these individuals. However, patients with mouth cancers

are unfortunately taken care of for sometime by physicians who are relatively inexperienced in the complexities of oral cancer and are too conservative in radiation therapy or surgery.

The most common precancerous lesion of the mouth is leukoplakia. In an individual with leukoplakia, all of the oral mucosa undergoes a change, but the localized area of leukoplakia is the most marked. The transition to malignancy is marked by chronic fissure, ulceration, a reddish elevated papule, or hardness of the tissues surrounding the leukoplakia. Papillomas of the mouth may turn malignant as may spots of oral mucosa that are constantly subject to trauma in individuals with ill-fitting dentures or rough tooth surfaces.

Epitheliomas of the cheek are usually of the squamous-cell type, and grossly appear red and fleshy; the patient can sometimes give a history of carrying a tobacco quid or betal nut quid at the site of the malignancy. Extensive lesions of the buccal mucosa are common in mouth cancer. These areas spread to either alveolus, hard palate or involve the angle of the mouth; occasionally the cheek is perforated. When seen by a competent therapist these malignant areas average 4 cm. in width.[11]

At this stage carcinomas are often ulcerative, burrowing and exposing bone while the papillary types are cauliflower-like.

"In general, it may be said that the growths of the cheek are fairly sensitive to radium, except when they are very superficial and of the leukoplakic type. The softer and more fleshy the growth, the more successful is radium likely to be."[15]

When the growth is of the hard indurative type, diathermy excision of the lesion seems to be the treatment of choice.[1,8,15]

However, it is good practice to embed radium at the periphery of the excised area at the time of operation. The Ontario, Canada, Cancer Centers treated 103 cases of buccal mucosa from 1934 to 1939, almost exclusively with Roentgen ray and radium, with a survival rate of 50%.[14]

If one wishes to attempt the control of a fungating malignant mass with radium alone, the bulk of the lesion may be easily reduced with a diathermy knife and thus permit the radium to be distributed more judiciously and economically. In lesions which are radiosensitive more reliance should be placed in radium than surgery.

"Epitheliomas of the cheek have a marked tendency to involve the cervical lymph nodes; and even though none of the regional nodes are palpably enlarged, this does not rule out the possibility of their being involved. Consequently, unless the local lesion is very small and very low grade, we believe a block dissection of the cervical lymph nodes is indicated whether or not the lymph nodes are involved clinically."[6] Where the primary has reached the alveolar process it is advisable to destroy the underlying bone by cauterization at the time of the combined excision and neck dissection.[1] Jorstad prefers not to do a routine neck dissection and awaits palpable nodes. On those cases which have freely movable nodes, and on which he did perform a submaxillary neck dissection, 66% were found to possess cancerous nodes—an important fact for those to be conscious of who are inclined to wait and hope that these freely movable nodes will turn out to be merely inflammatory glands. In 116 cases involving a buccal mucosa, alveolar process, palate and velum that were treated by excision alone, either with the knife or cautery, a 5 year survival rate of 34% was obtained. In those receiving a unilateral neck dissection in addition to care of the primary, the survival rate was raised to 53%.[8]

If radium treatment is decided upon, the physician should be conscious

of some general principles. "Radium implantation is greatly facilitated by a good general anesthetic, as a poor anesthetic renders accurate implantation difficult. Intratracheal anesthesia is the most suitable type with the tube passed through the nose leaving the mouth available to the therapist.[13] Postoperatively, the usual routine for prevention of bronchopneumonia should be instituted. The needles after implantation should have the eye end stitched into the adjacent tissue, thus preventing their loosening and dislodgment. The radium silks leading from the mouth may be kept fairly clean by passing them through a flexible rubber tube. If different strength needles are used, or if some are to be taken out sooner than others, silk threads of various colors should be used. An assortment of mouth gags for working in various areas of the mouth are necessary, but most important is a good light.

"The simplest type of radium needle implantation used in the mouth is the 'single plane implantation.' In this the area to be treated—about 1 cm. clear of the known lesion in every direction—is outlined with radium needles of normal linear intensity in some rectangular form. The center is then put in parallel lines of needles of one-half the normal linear intensity about 1 cm. apart, in accordance with Paterson-Parker dosage system. The dose to be given is calculated at 0.5 cm. from the plane. Thus a block of tissue the size of the plane and 1 cm. thick is irradiated to a select dosage."[13]

"Unless the plane has a very large area, it is wise to give a higher dosage when a single plane implantation is used, than would be the case where a bigger volume is being treated by a multiplane or volume technique." The effective range of this type of implantation is small, and it is not always possible to be sure of the extent of the lesion. As a rough working rule, it is both safe and wise to give doses of the order of 7000 r. in 7 to 10 days from medium-sized planes, and 7500 r. from small planes. A medium-sized implantation should only be given doses in the region of 6000 to 6500 r. in a similar period. Single plane implantation of larger areas, for example, the whole cheek, only tolerate smaller doses in the neighborhood of 6000 to 6500 r."[13]

If the single plane technique is to be used in the cheek it will be found much easier to insert the needles through the cheek rather than to attempt the corners of the mouth, because of their rotundity. The curvature of the cheek also makes vertical insertion more feasible than horizontal insertion. The 3 mg. needles of 4.5 cm. active length may be inserted upwards with a finger in the mouth steadying the cheek. Occasionally parotitis from perforation of the parotid duct is a sequela.[13]

A sandwich mold can also be used for cheek lesions near the mouth angles. Both parts of the mold are made of dental compound with the needles embedded in it. The radium mucosa distance of the intra-oral plane is 0.5 cm., while the radium skin distance is 1 cm. A winged nut holds the plates together, and a projection of the mold serves as a bite block to hold the mold in position. Where the malignancy of the cheek is near the bone of either jaw, a sequestrum may later form due to the death of the superficial plate of the jaw.[15]

"The prognosis of radium treated carcinomata of the cheek is good, so long as radiation is sufficient. A small burn is not of serious import, and can be treated later by diathermy. Under radiation, on the other hand, is certain to be followed by recurrence, and the recurrence may be resistant to radium treatment."[15] Martin has reported 40% of his cheek cases controlled after $2\frac{1}{2}$ years treated exclusively by radium.[12]

After several weeks following radiation there should be present a superficial ulcer of a wash-leather appearance covering the area larger than the original growth.

Again, in the malignancy of the tongue and floor of the mouth, the squamous cell epitheliomas far outnumber the occasional lymphosarcoma, adenocarcinomas and endotheliomas. These epidermoid carcinomas are usually found at the lateral border of the tongue, but sometimes are seen on the undersurface and spreading out involving the mouth floor. The cancers on the dorsum are often at the site of an old luetic scar. The tongue lesions usually are seen as ulcers with ragged edges "woody" to the touch, and hard at the base. The rubbery-like feel of fibrous scar tissue is absent here. Necrosis is present in the larger lesions, and this necrotic area is soft.[8] Tuberculosis, syphilis, fibromas, cysts, actinomycosis, blastomycosis and the angiomas must be borne in mind when a papillary form of tongue cancer is considered.

The trend in therapy in dealing with the floor of the mouth and tongue carcinomas is definitely veering toward radiation rather than surgery. However, Erich believes that "the larger malignant tumors of the tongue, those situated posteriorly, and those located on the ventral surface are best destroyed with surgical diathermy."[6]

The commonest site, that is, on the side of the tongue, fortunately is the easiest to treat. Somervell prefers a 4 cm. needle of 3 cm. active length with 2 mg. strength inserted into the anterior part of the tongue and tied over the dorsum of the tongue to 2.5 cm. needle of 1 mg. strength inserted in the back of the tongue and pushed forward. In this technique if the dosage is 1 mg. per 1 cc. of tissue, the needles are left in place for 10 days, but doubling the strength and halving the time is preferable.

Carcinoma of the back of the tongue is often a large soft mass extending to the epiglottis. This growth is usually very radiosensitive, but the insertion of the needles must be done cautiously in order that the patient does not aspirate a piece of the friable tissue to start a lung metastasis. The needle should be long and with a high dosage to shorten the time in the tissue. Insertion can be accomplished from below the jaw, between the facial artery and the angle of the mandible.

When the tip of the tongue is involved, because of its extreme mobility, excision is best with transverse insertion of short needles for radiation of the base. Speech will be little affected by this procedure.[15]

If radium seeds are to be used, 1.5 mc. seeds can be implanted 1 cm. apart. With this technique Jorstad and Verda report 90% of private patients, 30 in number, had no evidence of local recurrence or incomplete regression after 5 years, and in 55 indigent patients, 64% met the same criteria.[9]

Carcinoma of the tonsil and about the epiglottis is the most difficult to treat because of the early metastasis. The tonsil can be treated by insertion of long radium needles below the mucosa in front of the ramus of the mandible—introducing them through the skin and conjointly using Roentgen ray therapy with 400 kv. or greater.

In cases where the first treatment of radiation has not controlled the lesion, or the greater part of the tongue is involved, surgery should be considered.

When the floor of the mouth is involved, radium needles can be introduced from just within the mandible from the outside, and pointed vertically upward—also needles should be inserted parallel to the axis of the tongue from within the mouth. It is probable here that some sequestration of the mandible will result.[15]

If molds are to be used in the floor of the mouth lesions, they should be of the sandwich type with a radium mucosal distance of 0.5 cm. delivering 8000 r. and a skin radium distance of 2 cm. delivering 6000 r. The molds are worn only 8 hours daily for a period of 7 to 8 days.

At the Memorial Hospital of New York, carcinoma of the floor of the mouth is treated preferably by Roentgen ray, using a portal from 3 to 4 cm. in the majority of cases. The cylinder inserted into the mouth holds the tongue upward and backward, this because almost all floor lesions seem to center about the submaxillary duct orifice. Other factors are a target distance of 35 cm. and 200 kv. with 15 to 30 ma., and a filter of 0.5 mm. of copper plus 1 mm. of aluminum. Daily treatment or treatments at least 3 times weekly are given to a total dose of from 5000 to 7500 r. delivered within 20 days. The treatment commonly is supplemented by interstitial radon averaging only up to millicuries and not exceeding 6 mc.[16]

Roentgen therapy has been adopted in this institution because it is believed that interstitial radon seed and radium needle treatment results in too high an incidence of local radionecrosis and osteomyelitis. On the other hand, most roentgenologists will admit that Roentgen rays are ineffective in controlling mouth cancer in their hands.

When the lesion extends to the alveolus surgery is probably necessary.

When the cancer starts on the alveolar ridge and is superficial, H. E. Davis, J. H. Gilmore and M. Baker of Chicago, in a large series, have been able to completely control the lesion with interstial radon seeds or radium needle molds without clinical evidence of bone radionecrosis.[5] Where this complication has occurred, it can be easily cared for surgically, or by the use of zinc peroxide.[17]

In mandibular cancer, surgery gives the best prognosis. Either resection or wide destruction of the mandible should be performed. If the malignancy has spread to the antrum the sinus must be widely opened so that a radium mold may be used, or the involved region should be destroyed by cautery.

Cancer of the soft palate usually responds well to radiation therapy. The radon seeds may be implanted or contact Roentgen ray employed. In some cases a sandwich mold will be tolerated here and usually a radium plaque can be placed on the superior surface of the soft palate after topical anesthesia.

Hard palate lesions give a good prognosis with surgery.[1]

It is to be noted that the treatments thus far discussed have chiefly been surgical or radiation from radium or radon. An exception was the therapy of floor of the mouth lesions as handled in the New York Memorial Hospital. M. Cutler for several years has been particularly interested in carcinomas which are considered radioresistant. The more resistant area in the center of the lesion receives a greater dosage; from 3 to 5 r. are delivered per minute, and usually 3 fields are used in oral cancer. As much as 1400 r. have been administered in 2 sessions through a port 3 by 3 cm. When radium is used with this concentrated technique 10 gm. are used at a distance of 12.5 cm. with ports varying from 10 to 2 cm. in diameter. In a floor of the mouth squamous cell carcinoma the field used was 6 by 6 cm. and the 10 gm. of radium at a distance of 12.5 cm. was filtered through 1 mm. of platinum. A total of 120,000 mg. hr. was delivered in 12 days in 5000 mg.-hr. doses received twice daily. After $2\frac{1}{2}$ years the patient still had no recurrence.[3,4] It is still too early to evaluate this method of treatment.

With radiation therapy radionecrosis is not uncommon. This is generally painful, the involved area is very tender, healing is slow and sepsis and suppuration usually present. This discouraging picture can be changed by the use of surgery.

The primary lesion in mouth cancer has a good prognosis when cared for by a competent radiotherapist or surgeon trained in oral cancer surgery. However, whether or not the patient survives will in a large measure be determined by how the cervical lymph glands are treated. Distant metastasis is rare in mouth malignancies; the regional glands preventing the spread below the clavicles. A huge cauliflower-like lesion of long duration may have no metastasis, while a small ulcer of the mouth, hard to see, may have caused considerable neck metastasis in a short period. Brown and McDowell, after studying the literature, state that in the past 15 years no 5-year cure of proven malignancy of cervical nodes has been reported with external radiation technique—the only radiation cures being interstitial radiation following access surgery.[2] The burden of the care of the cervical metastasis is therefore the surgeon's lot.

"Block dissections of the neck were never a popular operation with the general surgeon. It is in a field in which he is not called on to work frequently. The procedure is a prolonged one, requiring patience, meticulousness, and enthusiasm about the ultimate result. An intimate knowledge of the anatomy of the neck is required. For these reasons block dissections of the neck have been in many instances a name only, rather than a true description of the method carried out."[10] The problem is, of course, as to when the block neck dissection should be performed. Kennedy quotes Phillips as finding 51.6% of the cases in which a block neck dissection was carried out to have malignant glands in buccal carcinoma, even though none of the cases had clinical nodes. Simmons found 34% of his cases of oral cancer had involved nodes in the series without palpable nodes.

Erich deals with the metastasis even before caring for the primary. Others, such as Butlin, have also handled patients in the same manner. There are two reasons for operating on the neck before caring for the cancer in the mouth: 1. A malignancy in the neck may suddenly change in a few weeks from an operable case to that of a so-called inoperable metastasis.

2. The patient will often not return following a seemingly controlled condition of the primary, and a large number of these will sometimes return later with an inoperable metastasis.

However, the majority of those experienced in oral cancer prefer to treat the mouth lesion first if radiation is to be the form of treatment, and then watch the site of the primary for several weeks in order to evaluate the control of the lesion. If they feel that the tumor is not responding to irradiation they then believe surgery of the neck and of the primary can be combined in one operative procedure. Somervell, who has had personal experience with over 1000 cases of mouth cancers, believes that operation does not have the unpleasant after-effects of radiation, and prefers it except for tongue, cheek and tonsillar lesions. If operations are found to be insufficient in his clinic, they are reënforced by the use of radium. He believes deep Roentgen ray therapy is very disappointing in mouth cases; however, he is probably too pessimistic, for in some institutions deep Roentgen ray therapy is believed to be useful. One must always remember that one cancer cell left behind will kill the patient; a small radium burn or extramutilation may inconvenience the patient, but may save his life.

The study of the statistics of those handling a large number of cases leads one to believe the safest procedure in cheek, tongue and floor of the mouth lesions is to do block neck dissection as early as possible, waiting only to see if the primary is controlled. This procedure should be adopted regardless if nodes are palpable or not. In the case of cheek lesions without palpable nodes, a suprahyoid neck dissection will probably be adequate. In floor or mouth and tongue lesions a complete block neck dissection from the clavicle upwards to the mandible must be undertaken to give the patient even any reasonable security. This should always be done if palpable nodes are present or not. These neck dissections can be done under intratracheal anesthesia or possibly with nerve block infiltration anesthesia. B. Freeman has collected over 500 cases of block neck dissection with the use of nerve block anesthesia, without a single fatality.[7]

"Finally I feel that we should also remember that our duty is to relieve suffering, and often we ought to put that before the actual saving of life. If euthanasia is to be the probable effect of an operation it may be the right thing to do it, and it is, in my opinion, almost better than insufficiency or neglect.

"Perhaps that consideration may make our operation more radical and effectual. There is no excuse for a surgeon who does a shoddy or insufficient operation for malignant disease, least of all in a hospital where radium is available to reinforce operative deficiencies. 'He's had about enough; we had better leave that little bit,' said with the kindest motives, in order to save an extra 2% risk of mortality, may make the death sentence of the patient."[15]

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BOOK REVIEWS AND NOTICES

AGEING AND DEGENERATIVE DISEASES. Edited by ROBERT A. MOORE, School of Medicine, Washington University. VOLUME XI OF BIOLOGICAL SYMPOSIA, A Series of Volumes Devoted to Current Symposia in the Field of Biology. Edited by JAQUES CATTELL. Pp. 242; 6 ills. Lancaster: Jaques Cattell Press, 1945. Price, $3.00.

THIS 11th volume, like its predecessors, presents a valuable symposium on an important and timely problem by men experienced in their subject. Of the 12 items, most are from the chemical or experimental laboratory, a few present philosophic or clinical considerations. The list follows: The Relation Between Etiology and Morphology in Degenerative and Sclerosing Arterial Disease, by W. C. Hueper; Arteriosclerosis and Lipid Metabolism, by Irvine H. Page; Research Work on Degenerative Disease, by William B. Kountz; The Glucose Tolerance in the Elderly Patient, by Lilli Hofstatter, Arthur Sonnenberg, and W. B. Kountz; Progeria, Report of a Case, by Alfred S. Schwartz and Jean V. Cooke; Effects of Lesions of the Autonomic Ganglia Associated With Age and Disease, on the Vascular System, by Prof. Albert Kuntz; The Rôle of the Pancreas in Arteriosclerosis, by Prof. Lester R. Dragstedt; Difficulties in Clinical Recognition of Degenerative Diseases, by Edward J. Stieglitz; Correlation of Clinical Knowledge in the Treatment of the Degenerative Diseases, by Prof. William J. Kerr; Age, Change, and the Adopted Life, by Prof. William de B. MacNider; Nutrition and Growth and Their Influence on Longevity in Rats, by John A. Saxton; Some Hormone Action in Relation to the Ageing Process, by Prof. Leo Loeb; Round Table Discussion. As might have been expected, first there is considerable fluctuation in merit in these presentations; and, second, none of the problems of ageing and degenerative diseases have been solved. Nevertheless, those interested in geriatrics —and what physician should not be—will find here much profitable reading.

E. K.

THE PSYCHOLOGY OF WOMEN. A Psychoanalytic Interpretation. By HELENE DEUTSCH, M.D., Associate Psychiatrist, Massachusetts General Hospital; Lecturer, Boston Psychoanalytic Institute. Foreword by STANLEY COBB, M.D., Bullard Professor of Neuropathology, Harvard University. Vol. 1. Pp. 399. New York: Grune & Stratton, 1944. Price, $4.50; Vol. 2, Motherhood. Pp. 498. Ib., 1945. Price, $4.50.

THE first volume presents a systematic picture of female instinctual development and its relation to the reproductive function. Emphasis is placed upon the individual emotional experiences and the conflicts connected with them. The aim of the volume is to explain the normal psychic life of women and their normal conflicts. The material forming the basis for the book includes not only the personal observations of the author but records of many other observers, hospital files and records of social agencies. The material is treated from 3 aspects: an exposition of the psychologic life of woman, an analysis of this life, and the non-feminine aspect of femininity. It leaves out of consideration the problem of motherhood. The curriculum of the medical student includes no time allotted to the study of the emotional conflicts of women, and yet the practitioner meets such problems almost daily. This volume by Deutsch includes many interesting observations upon the nature of the thinking of women, which should hold the attention of physicians who are brought into contact with the psychologic problems of their female patients.

The second volume, on Motherhood, deals primarily with the normal conflicts which occur in connection with sterility, abortion, pregnancy, delivery

and lactation. It also includes a consideration of the mother-child relationship, unmarried mothers, adoptive mothers and stepmothers. This book contains many instructive case records which deal with the everyday problems of the practising physician, and consequently should be very helpful to both the obstetrician and the general practitioner. The author treats at some length the question of psychogenic sterility. If the psychic state of the patient forbids the consummation of the sex act, the resulting sterility might well be considered of psychic origin. However, since recent studies are showing the existence of a high incidence of non-ovulation occurring in women who otherwise have been found to be normal, as are their husbands, the Reviewer must remain skeptical regarding the rôle played by the mind as the cause of sterility where intercourse is practised. D. M.

OFFICE ENDOCRINOLOGY. By ROBERT B. GREENBLATT, B.A., M.D., C.M., Professor of Experimental Medicine, University of Georgia School of Medicine; Director, Sex Endocrine Clinic, University Hospital, Augusta, Ga. Foreword by G. LOMBARD KELLY, M.D., Dean, University of Georgia School of Medicine. Second Ed. Pp. 243; many figs. Springfield, Ill.: Charles C Thomas, 1944. Price, $4.00.

THIS small volume is based upon a series of lectures delivered to a postgraduate class in office endocrinology. Two-thirds of the volume deal with the female, one-third with the male. The volume does not pretend to be comprehensive. Its brevity and its emphasis upon therapy should recommend it to the busy practitioner. Small volumes frequently brought up to date have a very definite place in the library of all practising physicians. D. M.

THE MEDICAL CLINICS OF NORTH AMERICA. Symposium on New Developments in Medicine. Pp. 561; 96 figs. Philadelphia: W. B. Saunders, 1945. $16 per year.

AN excellent and timely review of modern therapeutic agents and methods, this issue comprises clinics from 5 major medical centers in the United States. Of especial interest in the article on cirrhosis of the liver, in which is presented an enlightening and hopeful approach to a very difficult therapeutic problem. Correlated with this article is a clinic in which liver biopsy is elucidated as a safe and very helpful diagnostic procedure. Another clinic not to be missed is that on the diagnosis and treatment of various pleural effusions.

J. W.

THE MANAGEMENT OF OBSTETRIC DIFFICULTIES. By PAUL TITUS, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh; Secretary of the American Board of Obstetrics and Gynecology; Comdr. (MC) USNR, attached to Professional Division, Bur. Med. and Surg., Navy Dept., Washington, D. C. Pp. 1000; 426 ills. and 8 color plates. Third Ed. St. Louis: C. V. Mosby, 1945. Price, $10.00.

TITUS' excellent volume, in this 3rd edition, includes revisions in many subjects: Roentgen ray pelvimetry, toxemia, caudal anesthesia, the technique of extraperitoneal Cesarean section, and considers at some length the use of penicillin. To those who are familiar with the earlier editions the present one needs no recommendation. D. M.

THOUGHTS, DEEDS AND HUMAN HAPPINESS. By K. W. MONSARRAT. Pp. 123. London: Hodder & Stoughton, 1944. Price, $1.50.

THIS book which is a sequel to one that was chiefly an analysis of human self-expression, is for the most part concerned with the question: Upon what should we rely in planning for what we desire, and is there a principle of behavior worthy of our confidence? The chapters are, Self-Expression; The

Human Self's Performance; The Energy-Matter Puzzle; The Mind-Body Puzzle; Interpretive Events; The Relative Principle; The Earth and Its Inhabitants; The Living and Non-Living Puzzle; Evolution in the Animal Kingdom to Man; Judgments of Value; Design for Living.

The text is presented in a way that does not lend itself to review readily. The words "Sense" and "Intelligence" are prominent throughout the entire work. By the former is meant the ability which gives one views or pictures; the latter implies the interpretation of those views in terms of actions that have produced what the views show. Confidence in these as complements to our desires will afford verdicts that are reliable as to judgments on terrestrial affairs. Coördination, not compulsion, is urged. We should be generous to each other, even giving to the other the wherewithal for the life that he prefers. It should not be "live and let live," but "live and give."

At the time when man's greatest efforts are directed toward the killing of man and the destruction of property, this noble sentiment of universal generousness comes like a gleam of light piercing the world's encircling darkness.

N. Y.

HANDBOOK OF PRACTICAL BACTERIOLOGY, A GUIDE TO BACTERIOLOGICAL LABORATORY WORK. By T. J. MACKIE and J. E. MCCARTNEY. Seventh Ed. Pp. 720. Baltimore: Williams & Wilkins, 1945. Price, $5.00.

THE book is rather small, the pages being only $4\frac{3}{4}$ by $7\frac{1}{4}$ inches. The subject matter deals entirely with the practical aspects of bacteriology. In addition to bacteria it includes material on spirochetes, fungi, rickettsiæ, filterable viruses and animal parasites. While the book undoubtedly is of value to workers in the British Kingdom, workers in the United States will find little use for it as the procedures are different from those ordinarily used and regarded as "standard technic" in this country.

H. M.

REFRACTION OF THE EYE. By ALFRED COWAN, M.D., Professor of Ophthalmology, Graduate School of Medicine, University of Pennsylvania; Attending Ophthalmologist, Philadelphia General Hospital; Consulting Ophthalmologist, Council for the Blind and Supervising Ophthalmologist of the Department of Public Assistance, Commonwealth of Pennsylvania. Pp. 278; 172 engravings and 3 colored plates. Second Ed. Philadelphia: Lea & Febiger, 1945. Price, $4.75.

THIS 2nd edition is very similar to the first. The subject matter, as in the 1st edition, is divided into 19 chapters dealing chiefly with the theory of optics and clinical refraction. A few sections such as the one on Aniseikonia, the use of cycloplegia and the bibliography have been enhanced. Many paragraphs have been rewritten, but with very little change in text. The 2nd edition has the same size, but fewer pages than the first. There are more lines on each page so that the book is thinner.

F. A.

A HANDBOOK OF PSYCHIATRY. By LOUIS J. KARNOSH, B.S., Sc.D., M.D., Associate Clinical Professor of Nervous Diseases, School of Medicine, Western Reserve University; Director of Neuropsychiatry, City Hospital, Cleveland; Consulting Neuropsychiatrist, Cleveland Clinic; and EDWARD M. ZUCKER, A.B., M.D., Clinical Instructor in Nervous Diseases, Western Reserve School of Medicine; Associate in Neuropsychiatry at Cleveland City Hospital. Pp. 302; 40 figs. St. Louis: C. V. Mosby, 1945. Price, $4.50.

WRITTEN for the general practitioner and medical student, the more prominent positions in the book are given to the manic-depressive psychoses, involutional psychoses, schizophrenia, paranoid states, and the psychoneuroses. The organic reaction types include psychoses with syphilis of the central nervous system, the traumatic psychoses, psychoses with brain tumor and other brain diseases, psychoses with cerebral arteriosclerosis, and senile

psychoses. Included in the discussion on psychosomatic medicine are the effects of repressed feelings on bodily functions, factors in cardiac disorders, gastro-intestinal disturbances and respiratory disturbances, and organic susceptibility. Since most subjects with psychopathic personalities do not become interned in mental hospitals or jails, many showing this troublesome disorder are at large; and since the general practitioner must deal with them often, a more comprehensive consideration of these disturbers would prove helpful. The final chapters discuss psychiatry and the law and mental hygiene. The text finds fulfillment of the purposes stated in the Preface. A glossary is included. N. Y.

A Bibliography of Visual Literature. By John F. Fulton. Pp. 117. Springfield, Ill.: Charles C Thomas, 1945. Price, $3.00.

This book is patterned on the 2 volumes, "Bibliography of Aviation Medicine" which appeared in 1942 and 1944. It is extremely useful as a guide to recent literature, particularly as many of the articles abstracted are from other than ophthalmologic journals. Attention has naturally been concentrated on the biologic aspects of ophthalmology and the book does not intend to be complete in all phases of general ophthalmology or ocular pathology. The indexing is so complete that much time will be saved by anyone looking up the literature on a particular subject. F. A.

Doctors at War. Edited by Morris Fishbein, M.D. Pp. 418; fully illustrated. New York: E. P. Dutton, 1945. Price, $5.00.

This important statement of various aspects of the American Medical effort in the present war is made by 16 well qualified authorities. In a form of presentation that should interest both layman and medico, it gives a stirring picture of what American military and civil medicine are accomplishing today. As to selection of draftees, and their training, to men in action and rehabilitation, to the prevention and treatment of disease in the army, navy, industry and the home, the record is one of which we all may be proud—the one thing we should all know more about. Though good use is made of the 400 pages and one finds a considerable amount of factual and statistical matter included, the book could hardly be more than a bird's-eye view; but it is a good one and an authoritative well-balanced presentation of an important phase of the war effort, and one of which our profession and the country at large can be most proud. E. K.

NEW BOOKS

The History of Surgical Anesthesia. By Thomas E. Keys. With an Introductory Essay by Chauncey D. Leake and a concluding chapter, The Future of Anæsthesia by Noel A. Gillespie. Pp. 191. New York: Schuman's, 1945. Price, $6.00.

Bacillary Dysentery, Colitis and Enteritis. By Joseph Felsen, B.A., M.D., Director of Medical Research, Bronx Hospital, New York; Director of International and Pan-American Dysentery Registry. Pp. 618 with 145 ills.. Phila.: Saunders, 1945. Price, $6.00.

The Story of a Country Medical College. A History of the Clinical School of Medicine and The Vermont Medical College, Woodstock, Vt., 1827–1856. By Frederick Clayton Waite. Pp. 213. Montpelier, Vt.: Vermont Historical Society, 1945. Price, $4.50.

The Care of the Neurosurgical Patient—Before, During and After Operation. By Ernest Sachs, A.B., M.D., Professor of Clinical Neurological Surgery, Washington Univ. School of Medicine, Saint Louis, Mo. Pp. 268; 177 ills, including 2 in color. St. Louis: Mosby, 1945. Price, $6.00.

A Primer of Electrocardiography. By GEORGE BUPCH, M.D., F.A.C.P., Assoc. Professor of Medicine, Tulane Univ. School of Medicine; Senior Visiting Physician, Charity Hospital, New Orleans; and TRAVIS WINSOR, M.D., Instructor in Medicine, Tulane Univ. School of Medicine; Assistant Visiting Physician, Charity Hospital, New Orleans, La. Pp. 215; 235 engravings. Phila.: Lea & Febiger, 1945. Price, $3.50.

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